The American Journal of Cardiology®

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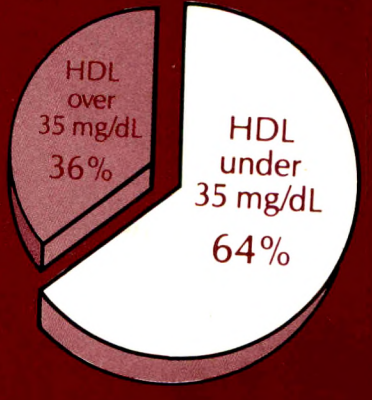
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JULY 1, 1991, VOL. 68, NO. 1

CORONARY ARTERY DISEASE

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Comparison of Serial Quantitative Evaluation of Calcified Coronary Artery Plaque by Ultrafast Computed Tomography in Persons With and Without Obstructive Coronary Artery Disease

Warren R. Janowitz, Arthur S. Agatston, and Manuel Viamonte, Jr.

This study evaluates the ability of ultrafast CT to follow the natural history of calcified coronary plaque. Serial studies were performed a mean of 406 days apart in 25 subjects: 10 with obstructive coronary artery disease, 10 without proved disease but with calcific deposits and 5 without disease or calcific deposits. Changes in calcified plaque area and volume, number of lesions, plaque density and total calcium score were measured. In subjects with calcific deposits, significant increases were seen in calcified plaque area and volume, mean CT number and total calcium score. Patients with obstructive disease had a greater number of new lesions than asymptomatic subjects with calcium ($p = 0.58$), as well as a greater increase in calcified plaque volume ($p < 0.001$). Ultrafast CT has the potential to follow noninvasively changes in coronary atherosclerosis in both obstructive and nonobstructive coronary artery disease.

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Evolution of Myocardial Ischemia and Left Ventricular Function in Patients With Angina Pectoris Without Myocardial Infarction and Total Occlusion of the Left Anterior Descending Coronary Artery and Collaterals from Other Coronary Arteries

Yves Juillière, Pierre Y. Marie, Nicolas Danchin, Gilles Karcher, Alain Bertrand, and François Cherrier

Myocardial ischemia and left ventricular (LV) function were assessed in 16 medically treated patients several years after documented well-collateralized left anterior descending coronary occlusion without myocardial infarction. One patient was lost at follow-up and 1 died (extracardiac death). The mean follow-up was 48 months. Ten patients had ≥1 sign of stress ischemia. However, all patients had a normal LV ejection fraction at rest. Collateral circulation preserves LV function at the time of coronary occlusion and, in some cases, prevents the development of myocardial ischemia; in patients with persisting myocardial ischemia after well-collateralized coronary occlusion, LV function is not impaired at long-term follow-up.

Continued on page A13

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Usefulness of Early Versus Late Programmed Ventricular Stimulation in Acute Myocardial Infarction

Akihiko Nogami, Kazutaka Aonuma, Atsushi Takahashi, Junichi Nitta, Yeong-Hwa Chun, Yoshito Iesaka, Michiaki Hiroe, and Fumiaki Marumo

To determine the influence of timing on the prognostic value of programmed ventricular stimulation after acute myocardial infarction (AMI), 32 patients were studied on days 19 and 36. Sustained monomorphic ventricular tachycardia (VT) was induced in 12 patients at the early study and in 8 at the late study. Both inducibilities of sustained monomorphic VT at the early ($p = 0.045$) and late studies ($p < 0.001$) were predictive of sudden cardiac death and subsequent arrhythmic events. However, inducibility of sustained monomorphic VT at the late study had a higher sensitivity, specificity, and positive and negative predictive values. Timing of programmed stimulation influences both the inducibility of VT and its predictive ability, with the later study being superior to the early study.

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Relation of Left Ventricular Volume and Function Over One Year After Acute Myocardial Infarction to Infarct Size Determined by Technetium-99m Sestamibi

Timothy F. Christian, Thomas Behrenbeck, Bernard J. Gersh, and Raymond J. Gibbons

Twenty patients with a first acute myocardial infarction who received successful reperfusion therapy had infarct size estimated at discharge using technetium-99m sestamibi tomographic imaging and radionuclide angiography at discharge, 6 weeks and 1 year. Perfusion defect size correlated with ejection fraction at all 3 time points ($r = -0.78$ to -0.081, p all <0.0001) as well as end-systolic volume index ($r = 0.63$ to 0.76, $p < 0.005$ to < 0.0001). Correlation of perfusion defect size with end-diastolic volume index was significant only at 1 year. There was no significant group change in ventricular volumes over 1 year and no relation of infarct size with individual changes in ventricular volumes. Technetium-99m sestamibi infarct size at discharge correlated with ejection fraction and ventricular volumes at 1 year. In patients with patent infarct arteries after acute myocardial infarction, there was no significant change in ventricular volumes as measured by radionuclide ventriculography.

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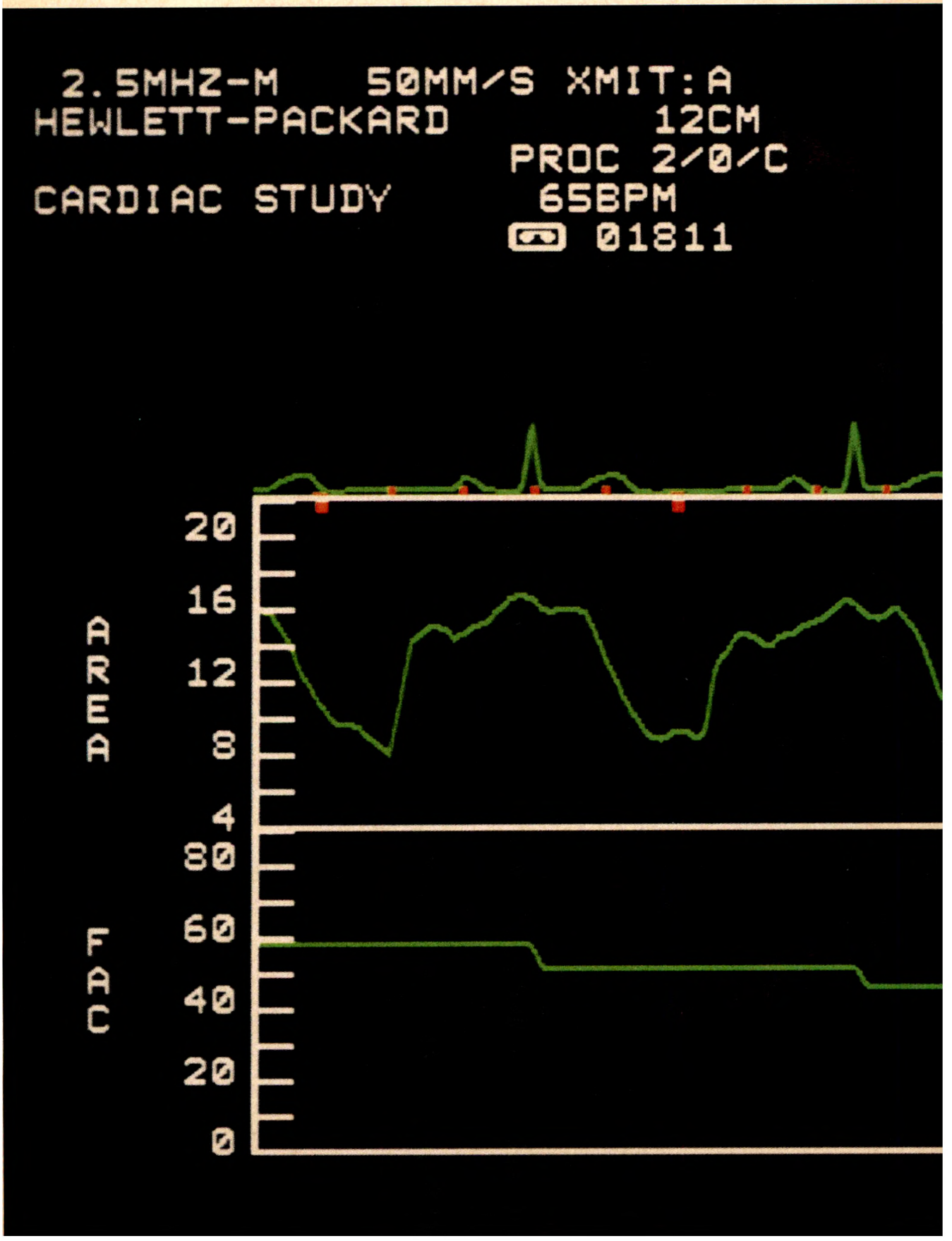
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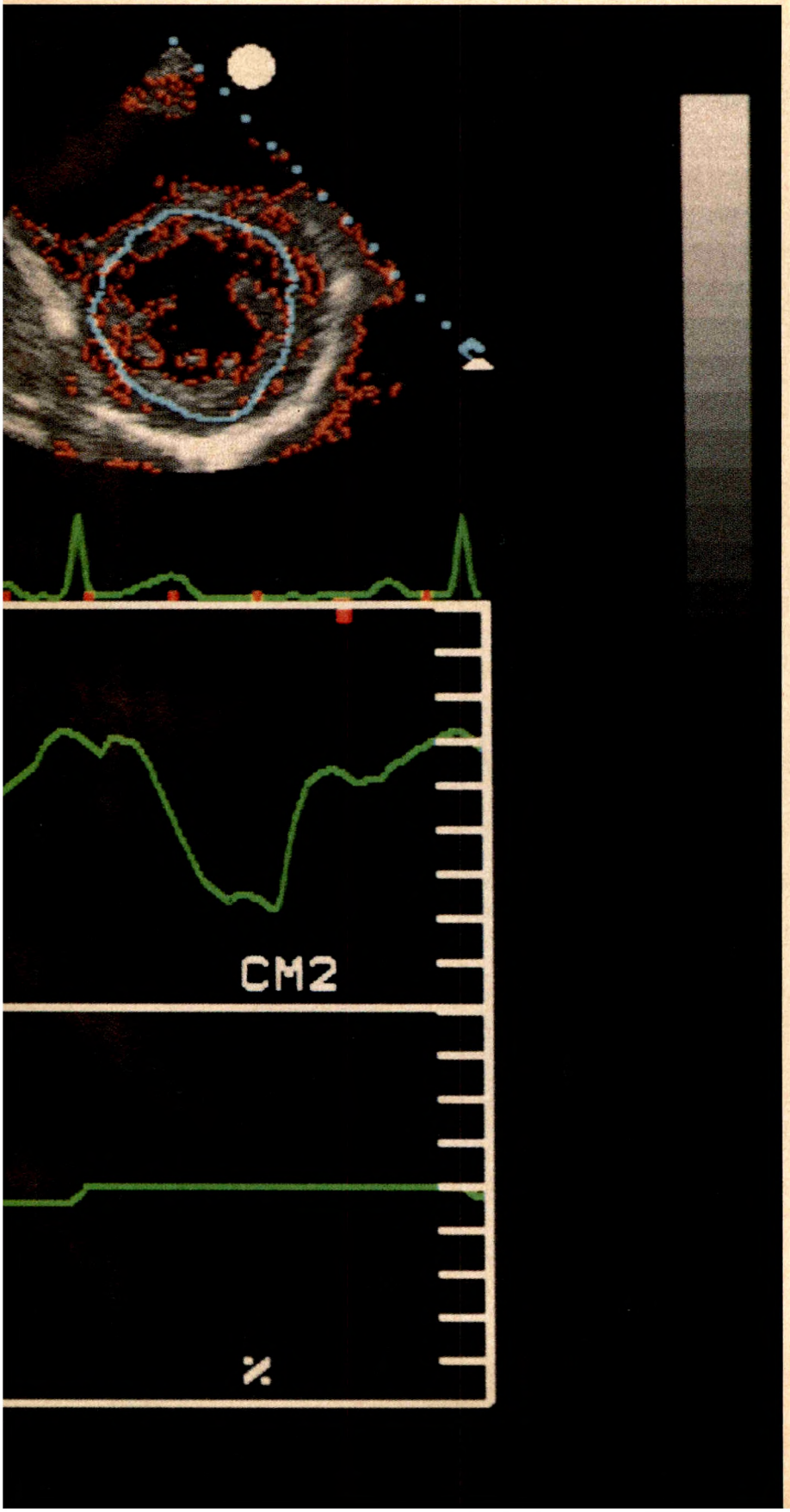
Stefan Jost, Dietrich Gulba, Werner G. Daniel, Ivo Amende, Rüdiger Simon, Sabine Eckert, and Paul R. Lichtlen

The influence of morphologic parameters on the angiographic recurrence of stenosis after percutaneous transluminal coronary angioplasty of 49 stenoses in aortocoronary venous bypass grafts in 41 patients was investigated. Angioplasty was successful in 46 stenoses (94%) of 38 patients (93%). Control coronary angiography performed in 35 patients (92%) with 42 stenoses after a mean interval of 189 ± 186 days revealed recur-

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rence of 9 stenoses (21%) in 9 patients (26%). In recurrent stenoses, the diameter of the grafted coronary artery distal to the anastomosis was significantly smaller than in grafted arteries without recurrent stenoses (1.92 ± 0.52 vs 2.45 ± 0.50 mm; $p < 0.01$). Recurrence also correlated with the stenosis length of >10 mm before angioplasty ($p < 0.01$). Graft age, graft diameter and stenosis location in the graft had no influence on recurrence. Thus, the diameter of the grafted coronary artery and the length of the critical stenosis are parameters for recurrence of graft stenoses after angioplasty.

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Effects of a Multidimensional Cardiopulmonary Rehabilitation Program on Psychosocial Function

Kathleen Dracup, Debra K. Moser, Celine Marsden, Shelley E. Taylor, and Peter M. Guzy

The effects of participation in a structured, outpatient cardiac rehabilitation program on psychosocial function after acute myocardial infarction and coronary artery bypass surgery, or both, were evaluated prospectively in 141 cardiac patients who were married or living with a "significant other" (89% men, mean age 63 ± 9 years old). Forty-one patients who were participants in a 3-month cardiac rehabilitation program were compared with 100 patients who did not participate in a formal program. Patients in the 2 groups were not different at baseline in sociodemographic or clinical characteristics or in any of the dependent measures. Six months after initial testing, patients who attended cardiac rehabilitation were significantly less anxious, less depressed, had better psychosocial adjustment to illness, and were more satisfied with their marriages than nonparticipants.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Efficacy and Safety of Intravenous Sotalol for Termination of Paroxysmal Supraventricular Tachycardia

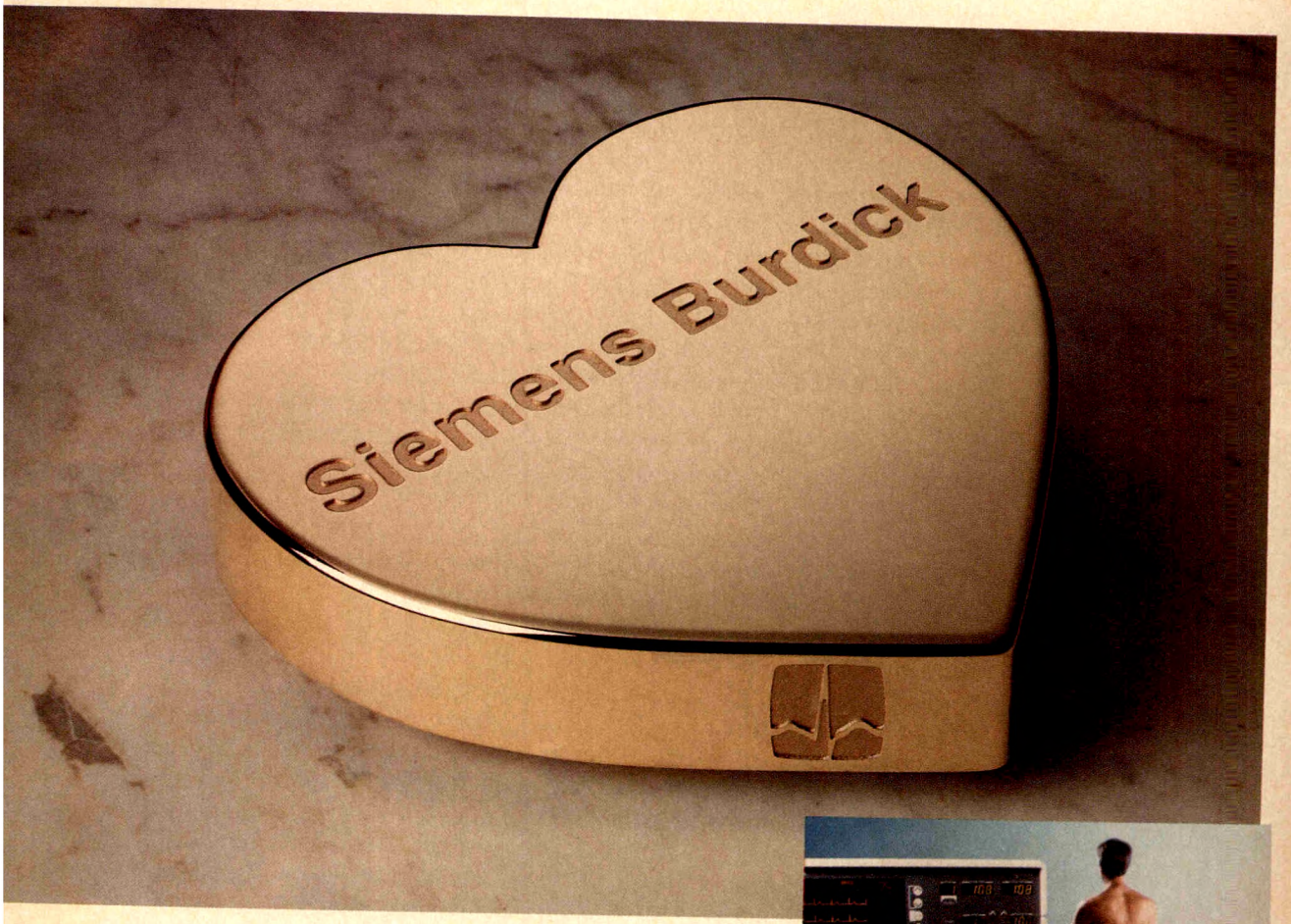
Luc Jordaens, Anton Gorgels, Roland Stroobandt, and Jacques Temmerman

In 43 patients with paroxysmal supraventricular tachycardia, a double-blind, placebo-controlled, crossover multicenter study was conducted to study the efficacy and safety of intravenous sotalol (1.5 mg/kg over 10 minutes) in terminating the arrhythmia. Normal sinus rhythm was achieved within 30 minutes in 83% of all patients who received sotalol as the first drug, compared with 15% of the patients who received placebo ($p < 0.0001$). The drug was active in spontaneous tachycardia as well as in induced tachycardia; the type of arrhythmia (atrioventricular nodal reentry vs circus movement tachycardia) was not important for the outcome. The intravenous administration of sotalol was also safe and was not associated with proarrhythmic events.

Continued on page A20

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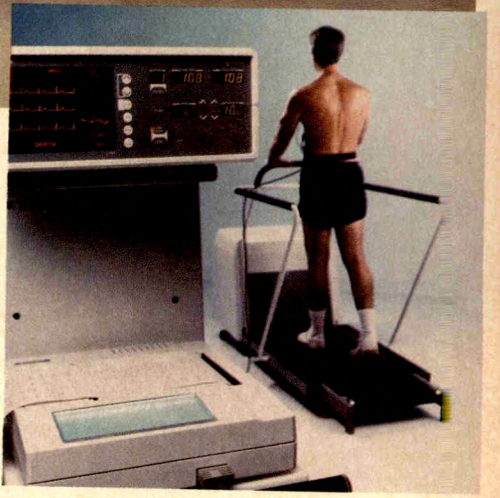
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41
Prediction of Uneventful Cardioversion and Maintenance of Sinus Rhythm from Direct-Current Electrical Cardioversion of Chronic Atrial Fibrillation and Flutter
Isabelle C. Van Gelder, Harry J. Crijns, Wiek H. Van Gilst, Remco Verwer, and Kong I. Lie

The present study was undertaken to reassess prospectively the immediate and long-term results of direct-current electrical cardioversion in patients with chronic atrial fibrillation or atrial flutter, and to determine factors predicting clinical outcome of the arrhythmia after cardioversion. Two-hundred forty-six patients underwent electrical cardioversion and were followed during a mean of 260 days. Stepwise logistic regression analysis revealed that arrhythmia duration ($p < 0.001$), type of arrhythmia ($p < 0.02$) and age ($p < 0.05$) independently influenced conversion rate. Multivariate regression analysis revealed that the type of arrhythmia ($p = 0.0008$), low precardioversion functional class ($p = 0.002$) and the presence of nonrheumatic mitral valve disease ($p = 0.03$) independently increased the length of the arrhythmia-free episode. Rheumatic heart disease shortened this period ($p = 0.03$). In conclusion, patients having a high probability of conversion together with a prolonged post-shock arrhythmia-free episode can be identified before cardioversion. This may improve the cost-benefit ratio of this procedure.

47
Clinical and Angiographic Observations on Resuscitated Victims of Exercise-Related Sudden Ischemic Death
Renzo Ciampricotti, Rob Taverne, and Mamdouh El Gamal

To elucidate the mechanism(s) of exercise-related sudden ischemic death, we report the clinical and angiographic findings of 17 survivors of sudden death related to sport ($n = 10$) and to an exercise test ($n = 7$). Cardiac arrest occurred in most cases without prior warning symptoms and was associated with acute myocardial infarction in 10, with unstable angina in 5 and with silent ischemia in 2. Acute coronary angiographic studies in 15 patients revealed subtotal or total occlusion of most of the ischemia-related arteries. Exercise-related sudden ischemic death can be caused by an acute coronary event. Exercise itself can unexpectedly provoke such an event, probably by inducing intracoronary changes.

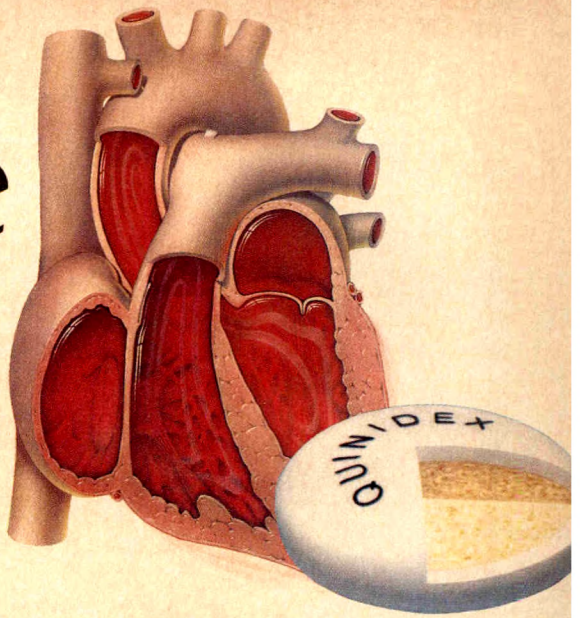
SYSTEMIC HYPERTENSION

51
Left Ventricular Diastolic Filling Alterations in Normotensive Young Adults with a Family History of Systemic Hypertension
William F. Graettinger, Joel M. Neutel, David H.G. Smith, and Michael A. Weber

To characterize the cardiovascular consequences of a history of hypertension in normotensive young adults, 72 volunteers (aged 18 to 30 years) were studied with Doppler echocardiography and blood pressure (BP) monitoring. Nineteen (12 men) with a family history of hypertension were

Continued on page A22

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital), phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 5 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter, torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

compared with systolic BP in gender-matched controls. There were no differences in 2-hour BP, left ventricular mass or systolic function. More prominent late diastolic filling was observed with a family history of hypertension. Late diastolic flow time and integral were greater (132 ± 24 vs 117 ± 17 ms, $p < 0.05$ and 2.5 ± 0.7 vs 1.9 ± 0.5 cm, $p < 0.01$). The 12 men with a family history of hypertension had greater late (40 ± 0.9 vs 31 ± 0.8 cm/s, $p < 0.02$) and ratio of late-to-early (0.64 ± 0.19 vs 0.46 ± 0.10, $p < 0.01$) flows and velocity integrals (2.6 ± 0.8 vs 1.9 ± 0.5 cm, $p < 0.05$). In contrast, the women differed only in longer late diastolic flow time with family history (129 ± 11 vs 109 ± 20 ms, $p < 0.05$). The findings in women with a family history of hypertension may reflect later onset of hypertension and related cardiovascular changes. In young normotensive men with a family history of hypertension, left ventricular filling, although normal, shifted toward that observed in hypertensives and may represent early inherited characteristics of the hypertension syndrome.

57

Left Ventricular Filling in the Systemic Hypertension of Obesity

Ehud Grossman, Shmuel Oren, and Franz H. Messerli

Cardiac structure and systolic as well as diastolic functions were evaluated by 2-dimensional M-mode echocardiography in lean and obese patients who were either hypertensive or normotensive. Diastolic function, as assessed by diminished normalized early peak filling rate and prolonged duration of rapid filling, was decreased in hypertensive patients compared with normotensive patients ($p = 0.02$). When compared with lean patients with similar blood pressure levels, obese patients exhibited a lower normalized peak filling rate ($p = 0.0014$) but no difference in duration of rapid filling. A significant correlation was observed between the normalized peak filling rate and either body mass index or left ventricular (LV) mass ($r = 0.355$ and $r = -0.32$, respectively; $p < 0.001$). Impairment of LV filling was most pronounced in obese hypertensive patients. It is concluded that the burden on the left ventricle imposed by obesity causes cardiac enlargement and impairment of LV filling regardless of levels of arterial pressure.

61

Effect of Bisoprolol on Blood Pressure and Arterial Hemodynamics in Systemic Hypertension

Risk G. Asmar, Jean C. Kerihuel, Xavier J. Girerd, and Michel E. Safar

Common carotid and brachial arterial hemodynamics using pulsed Doppler flowmetry and pulse wave velocity were evaluated using a double-blind crossover design versus placebo in patients with sustained essential hypertension treated with a selective β_1 blocking agent bisoprolol. Blood pressure and heart rate significantly decreased after administration of bisoprolol, whereas no significant change occurred in the diameter, the blood flow and in the vascular resistance of the carotid and brachial circulations. Pulse wave velocity significantly decreased in the brachioradial and the carotid femoral areas. Brachial artery compliance significantly increased, indicating that the antihypertensive effect of β_1 blockade is associated with an improvement in the viscoelastic properties of the arterial wall.

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65
Cardiovascular Effects of Isradipine in Essential Hypertension
Ehud Grossman, Franz H. Messerli, Shmuel Oren, Boris Nunez, and Guillermo E. Garavaglia

The cardiovascular effects of oral isradipine therapy were evaluated in mild to moderate hypertension. Isradipine reduced arterial pressure through a decrease in total peripheral resistance but without causing an increase in heart rate or cardiac output or activating the sympathetic nervous system. Isradipine reduced left ventricular mass and improved cardiac contractility and left ventricular filling. Renal blood flow increased, and renal vascular resistance ($p < 0.01$) and total blood volume ($p < 0.002$) decreased without a change in either sodium excretion or body weight. Thus, isradipine reduced arterial pressure by reducing total peripheral resistance without activation of reflexive mechanisms. Its effects on systemic hemodynamics, total blood volume, renal blood flow, and cardiac structure and function make isradipine an excellent choice for antihypertensive therapy.

CONGESTIVE HEART FAILURE

71
Difference in Mortality Between Patients Treated with Captopril or Enalapril in the Xamoterol in Severe Heart Failure Study
Hubert Pouleur, Michel F. Rousseau, Celia Oakley, and Lars Rydén, for the Xamoterol in Severe Heart Failure Study Group

Difference in probability of survival was detected between patients treated with captopril or enalapril in the Xamoterol in Severe Heart Failure Study. These differences did not appear to be caused by a greater severity of heart failure in the captopril group but could be related to different degrees of angiotensin-converting enzyme inhibition between the 2 treated groups. Future clinical trials must determine to what extent complete circadian angiotensin-converting enzyme inhibition is necessary to provide the full benefit of this therapy in heart failure.

VALVULAR HEART DISEASE

75
Determinants of One-Year Outcome from Balloon Aortic Valvuloplasty
Charles J. Davidson, J. Kevin Harrison, Karen S. Pieper, Michael Harding, James B. Hermiller, Katherine Kisslo, Cynthia Pierce, and Thomas M. Bashore

Previous studies with balloon aortic valvuloplasty (BAV) have been unable to predict 1-year outcome because of limited acute and follow-up clinical, invasive and echocardiographic data. The purpose of this study was to predict long-term outcome based on comprehensive data obtained at the time of valvuloplasty and at 3 and 6 months after the procedure. Of

the 170 consecutive patients undergoing BAV, 108 (mean age 78 years) were eligible for 1-year follow-up. Prospective clinical, macromanometer hemodynamic, digital ventriculographic, and echocardiographic/Doppler data were collected at baseline and immediately after the procedure. Echocardiographic data were also obtained at 3 and 6 months. Using Cox model analysis, major events were predicted by advanced age, baseline heart failure class, and baseline echocardiographic-determined diastolic left ventricular diameter. Only baseline left ventricular ejection fraction proved to be a significant predictor of cardiac death in a multivariate model. Absolute values and acute changes after BAV measured by catheterization or echocardiogram did not provide additional predictive information over that of ejection fraction after the procedure. Similarly, echocardiographic valve area and transvalvular gradient at 3 months added no further prognostic data. Thus, prognosis after BAV can be determined by noninvasive clinical and echocardiographic data obtained before cardiac catheterization. Despite advanced age and co-morbid disease, BAV patients with a baseline ejection fraction ≥45% have an excellent 1-year cardiac survival.

81

Relation Between Myocardial Beta-Adrenergic Receptor and Left Ventricular Function in Patients With Left Ventricular Volume Overload Due to Chronic Mitral Regurgitation With or Without Aortic Regurgitation

Nobuo Sakagoshi, Susumu Nakano, Kazuhiro Taniguchi, Nobuaki Hirata, and Hikaru Matsuda

The relation between myocardial β-adrenergic receptor and left ventricular (LV) function was studied in 10 patients with LV volume load due to chronic mitral regurgitation with or without aortic regurgitation (AR). Beta-adrenergic receptor density in 7 patients with New York Heart Association class II or III congestive heart failure was higher than that in 3 patients with class IV heart failure. Beta-adrenergic receptor density showed a positive correlation with end-systolic stress/end-systolic volume index ratio, the index for contractile function. The results demonstrated that worsening in symptom and LV dysfunction, particularly of the contractile state, was associated with decreased myocardial β-adrenergic receptor density from possible down-regulation in patients with chronic mitral regurgitation with or without aortic regurgitation.

CARDIOMYOPATHY

85

Echocardiographic Evidence for the Existence of a Distinct Diabetic Cardiomyopathy (The Framingham Heart Study)

Maurizio Galderisi, Keaven M. Anderson, Peter W.F. Wilson, and Daniel Levy

The contribution of diabetes and glucose intolerance to age-adjusted echocardiographic parameters of Framingham Heart Study subjects was examined. Subjects with evidence of cardiovascular disease were excluded. Diabetic women had significantly increased left ventricular (LV) wall

Continued on page A31

thickness, relative wall thickness, LV end-diastolic dimension and LV mass. Women with glucose intolerance showed similar, less significant trends. In diabetic men fractional shortening was slightly reduced. In a multivariate model that included potentially confounding factors, diabetes remained an independent contributor to LV mass and wall thickness in women. In conclusion, our data support the existence of a distinct diabetic cardiomyopathy in women.

CONGENITAL HEART DISEASE

90

The Changing Pattern of Infective Endocarditis in Childhood

Sami M. Awadallah, Rae-Ellen W. Kavey, Craig J. Byrum, Frank C. Smith, Daniel A. Kveselis, and Marie S. Blackman

Forty-eight cases of infective endocarditis (IE) in 42 patients with congenital heart disease were reviewed from 1970 through 1990 and compared with a 20-year review of 108 cases diagnosed between 1953 and 1972. The review demonstrates that the natural history of IE in children has changed over the last 2 decades. Half of the cases occurred after surgery for congenital heart disease. In 29% of this subgroup, the site for IE was a right ventricular to pulmonary artery valved conduit. Among patients with nonsurgically treated congenital heart disease and IE, mitral valve prolapse has emerged as an important underlying heart lesion occurring in 29% of patients. The bacterial spectrum has shifted with a significant increase in the incidence of uncommon causative organisms. Mortality has continued to decline, with survivorship of 90% in this series.

MISCELLANEOUS

95

Abnormal Left Ventricular Diastolic Filling in Eccentric Left Ventricular Hypertrophy of Obesity

Simon Chakko, Manuel Mayor, Mark D. Allison, Kenneth M. Kessler, Barry J. Materson, and Robert J. Myerburg

With use of pulsed-wave Doppler echocardiography, left ventricular (LV) diastolic filling was studied in 11 obese, normotensive patients with eccentric LV hypertrophy, in 10 normal control subjects, and in 18 nonobese, hypertensive patients with concentric LV hypertrophy, whose antihypertensive medications were stopped before the study. Obese patients had a higher peak velocity of atrial filling, lower early/atrial filling velocity ratio, prolonged deceleration half-time and lower peak filling rate than normal control subjects. The deceleration half-time correlated with the body mass index. These diastolic filling abnormalities seen in obese patients were similar to those of hypertensive patients. Eccentric hypertrophy of obesity causes an abnormal LV filling pattern.

Continued on page A35



CAPOTEN (captopril tablets) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

METHODS

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Effects of Handrail Support on Claudication and Hemodynamic Responses to Single-Stage and Progressive Treadmill Protocols in Peripheral Vascular Occlusive Disease
Andrew W. Gardner, James S. Skinner, and L. Kent Smith

The effect of handrail support on claudication and hemodynamic responses to exercise were examined during repeated single-stage and progressive treadmill protocols in 10 patients. During both protocols, claudication pain distance and maximal walking distance increased on repeated tests with handrail support, whereas no change occurred without support. In contrast, foot transcutaneous oxygen tension, ankle systolic pressure and ankle/brachial systolic pressure index were not affected by support. Because the claudication variables were altered, handrail support should not be allowed when assessing claudicants, unless balance cannot otherwise be maintained.

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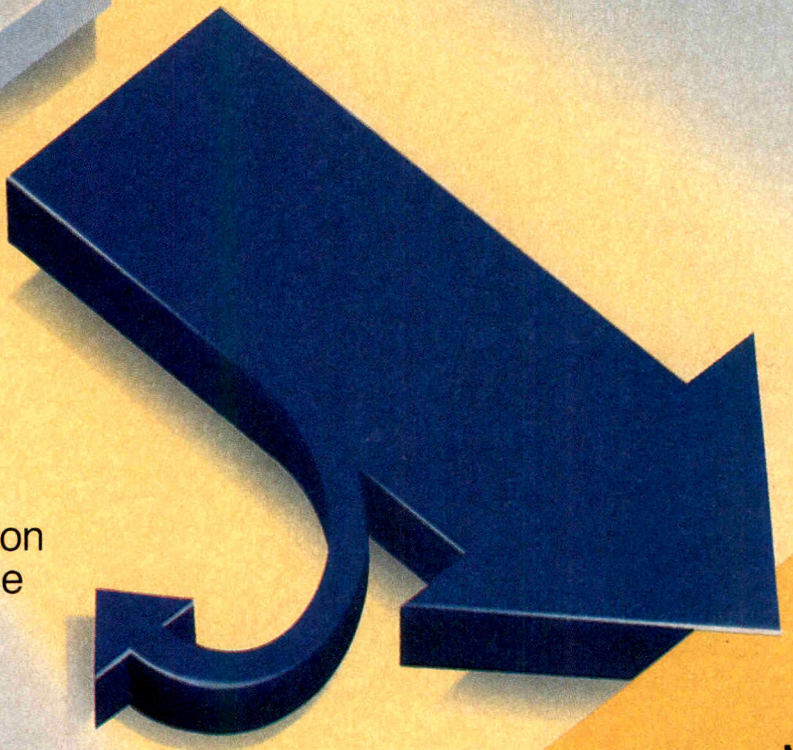
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For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

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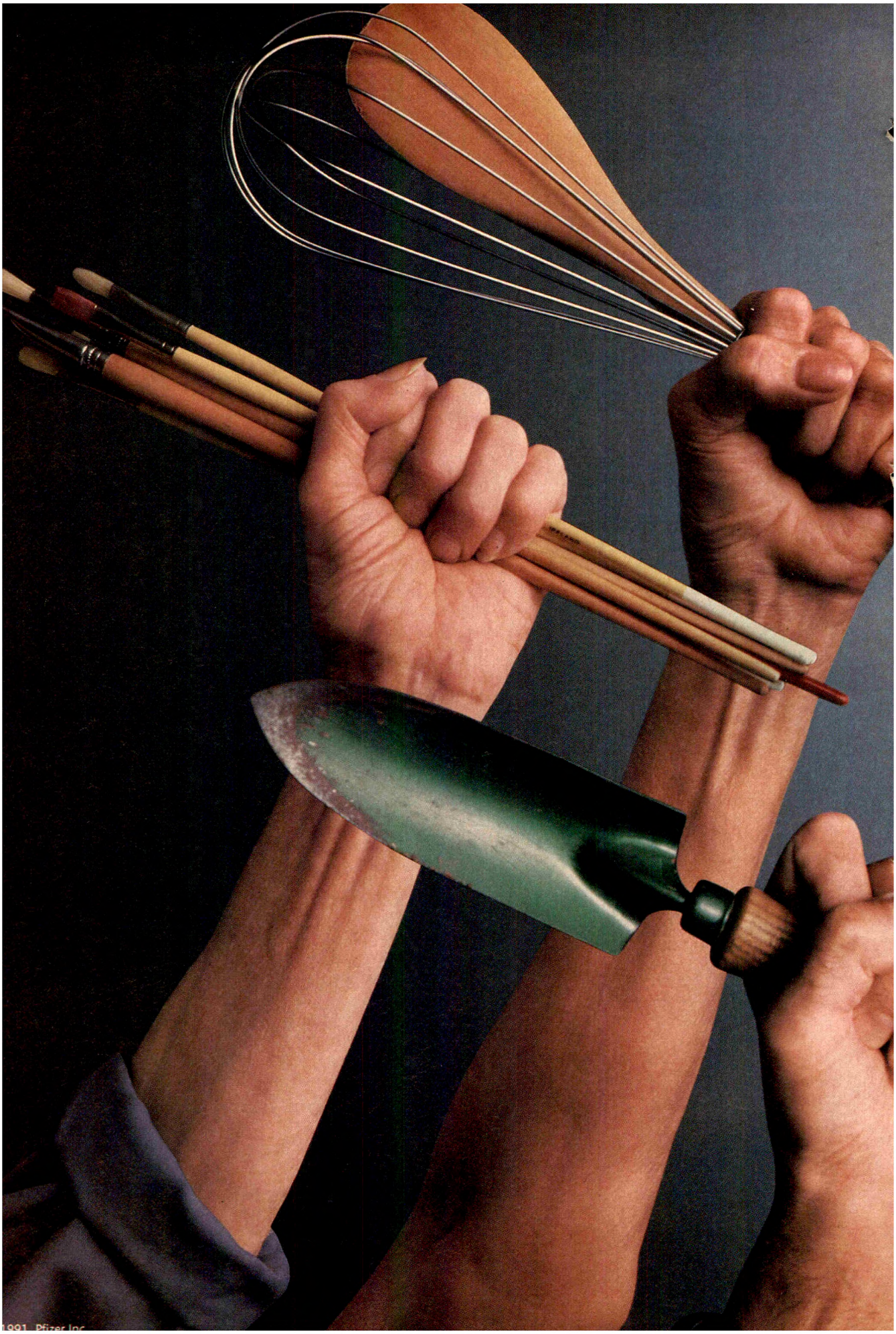
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FROM THE EDITOR

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The Government is in *Your* Office and Listening to *Their* Script
William C. Roberts

CLASSIFIED ADVERTISING on pages A4, A65, A66

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F SUMMARY

ATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of tension, alone or in combination with other antihypertensive drugs, and for the nent of salt and fluid retention associated with congestive heart failure.
in Pregnancy: See PRECAUTIONS.

RAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-d drugs.

NINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring ential. In general, diuretics should not be given with lithium.

AUTIONS: Perform serum electrolyte determinations at appropriate intervals. ially in patients who are vomiting excessively or receiving parenteral fluids, in ts subject to electrolyte imbalance, or in patients on a salt-restricted diet. In on, patients should be observed for clinical signs of fluid or electrolyte imbalance, as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of kalemia secondary to diuresis and natriuresis is increased with larger doses, with diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or . Interference with adequate oral intake of electrolytes will also contribute to kalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the effects of digitalis, such as increased ventricular irritability.
onal hyponatremia may occur in edematous patients; appropriate treatment is y water restriction. In actual salt depletion, appropriate replacement is the ment of choice. Chloride deficit is usually mild, not requiring specific treatment t in extraordinary circumstances (liver, renal disease).
ruricemia may occur, and frank gout may be precipitated in certain patients ving indapamide. Serum concentrations of uric acid should be monitored dically.
with caution in patients with severe renal disease; consider withholding or ntinuing if progressive renal impairment is observed. Renal function tests should rformed periodically.
with caution in patients with impaired hepatic function or progressive liver disease. minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
t diabetes may become manifest and insulin requirements in diabetic patients be altered during thiazide administration. Serum concentrations of glucose should onitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

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References: 1. Horgan JH, O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response to indapamide. *Postgrad Med J* 1981;57(Suppl 2): 64–67. **2.** Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258–262. **3.** Weidmann P, Meier A, Mordasini R, et al: Diuretic treatment and serum lipoproteins: Effects of tienilic acid and indapamide. *Klin Wochenschr* 1981;59:343–346. **4.** Meyer-Sabellek W, Gotzen R, Heitz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(Suppl II):170–174. **5.** Scalabrino A, Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17–22.

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Comparison of Serial Quantitative Evaluation of Calcified Coronary Artery Plaque by Ultrafast Computed Tomography in Persons With and Without Obstructive Coronary Artery Disease

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Coronary artery calcium indicates atherosclerosis. Ultrafast computed tomography (CT) can noninvasively visualize and quantify coronary calcium, permitting the natural history of calcified plaque to be studied. This pilot study evaluates the ability of ultrafast CT to follow the progression of calcified plaque within the coronary arteries in patients with and without obstructive coronary artery disease (CAD).

Twenty-five subjects had serial ultrafast CT scans of the coronary arteries a mean of 406 days apart. Changes in the number of calcific deposits, calcified plaque area and volume, calcium density and total calcium score were measured.

In the 20 patients with calcium on the first study, there were statistically significant increases in mean peak CT number, total calcified plaque volume, total calcified plaque area and total calcium score ($p < 0.0001$ for all). Subjects with proved obstructive CAD ($n = 10$) on angiography had a 48% increase in calcified plaque volume compared with 22% in asymptomatic subjects ($n = 10$). Comparison of serial studies showed that smaller calcific deposits often coalesced into single larger calcific deposits. Ninety-eight percent (235 of 241) of deposits identified on the first study were accounted for on the second study. Patients with obstructive CAD had a higher number of new calcific deposits than did those in the asymptomatic group (55 vs 18, $p = 0.058$). Serial ultrafast CT accurately tracks the progression of coronary artery calcium. It is a useful technique for assessing changes in calcified plaque formation in both asymptomatic subjects and in patients with obstructive CAD. It may be useful for studying the natural history of CAD and the effects of intervention on the course of CAD.

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Coronary artery calcium, unlike peripheral arterial calcium, is seen only in the presence of calcified atherosclerotic plaque.[1,2] When seen by fluoroscopy, it was found to be an independent risk factor for future coronary events.[3] A sensitive and accurate method for detecting and following the presence and extent of coronary calcium could be used to identify patients at risk of coronary artery disease (CAD) and follow the effects of risk factor interventions on the rate of progression of atherosclerosis.

Fluoroscopy and routine chest radiography have been used to detect coronary calcium. The presence of calcium by fluoroscopy correlates with the presence of obstructive CAD,[4–8] but fluoroscopy is rarely used now in clinical practice because its predictive value is perceived to be lower than other available procedures.

Other techniques have been used to detect coronary calcium with the goal of detecting obstructive and nonobstructive CAD. Digital subtraction fluoroscopy has an improved sensitivity and specificity compared with routine fluoroscopy.[9] Conventional computed tomography (CT), which has greater contrast resolution than fluoroscopy, has also been used.[10–13] These techniques are either operator-dependent or lack the temporal, contrast or spatial resolution necessary to detect small areas of calcium.

There are no published studies describing the natural history of coronary calcium in humans because of the lack of a reproducible technique that can image and

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TABLE I Study Group Composition and Number of Calcific Deposits

Pt. No.	Age (Yr)	Days Between Studies	Calcific Deposits First Study	Calcific Deposits Second Study	New Calcific Deposits
			Group I		
1	59	374	0	0	0
2	53	379	0	0	0
3	40	389	0	0	0
4	41	379	0	0	0
5	52	371	0	0	0
Mean	49 ± 7	378 ± 6	0	0	0
			Group II		
6	63	403	11	10	0
7	48	363	11	11	0
8	50	550	1	1	0
9	63	366	2	2	0
10	62	533	2	4	2
11	52	379	2	6	4
12	62	382	8	7	2
13	45	420	6	9	4
14	58	364	10	13	5
15	44	391	1	2	1
Mean	55 ± 7	415 ± 65	5.4 ± 4	6.5 ± 4	2 ± 2
			Group III		
16	55	491	10	13	2
17	63	427	6	8	3
18	49	361	20	24	9
19	78	393	20	38	18
20	43	416	17	23	3
21	45	376	16	21	8
22	63	475	35	31	4
23	59	363	32	31	2
24	59	374	16	26	6
25	59	441	15	12	0
Mean	57 ± 10	411 ± 44	19 ± 9	23 ± 9	5.5 ± 5

quantify coronary calcium. We recently described such a technique using ultrafast CT that scans the coronary arteries with high temporal, contrast and spatial resolution; it is more sensitive than fluoroscopy and can quantify coronary calcium.[14] Each image is obtained during the same portion of the cardiac cycle, allowing 3-dimensional images of the coronary anatomy to be reconstructed.

This pilot study evaluates the capability of serial ultrafast CT studies, performed approximately 1 year apart, for documenting the changes that occur in calcified coronary artery plaque. The natural history of calcified plaque in subjects with and without proved obstructive CAD is described. The value of 3-dimensional reconstructions to evaluate the presence and progression of coronary calcium is also presented.

METHODS

Patients: Twenty-five subjects (23 men, 2 women), who underwent ultrafast CT studies a mean of 406 days apart, were evaluated. The subjects were not part of a formal study protocol but were the first group of subjects to have serial ultrafast CT studies performed. Ten patients had angiographically proved obstructive CAD (2 patients with obvious motion in 1 study were excluded from analysis). An equal number of asymptomatic subjects with coronary calcium on the first study were chosen for detailed analysis. The patients were divided into 3 groups (Table I). Group I consisted of 5 asymptomatic patients with no coronary calcium on the first study. Calcium was seen in subjects in groups II and III on the first study. Group II consisted of 10 patients with no history or symptoms suggestive of ischemic heart disease and with negative exercise test results. Group III consisted of 10 patients with angiographically documented obstructive CAD. Because no patient in group I developed coronary artery calcium in the follow-up study, only the subjects in groups II and III were included in the analysis of the changes in number of calcified lesions, total calcium score, calcified plaque area and volume, and number of new calcific deposits. There was no significant difference in the age distributions of groups II and III.

Ultrafast computer tomography scans: Ultrafast CT studies were performed using an Imatron C-100 computed tomographic scanner as described previously.[14] Twenty contiguous, 3-mm-thick slices were obtained through the base of the heart including the proximal coronary arteries. Scan time was 100 ms per image with electrocardiographic triggering to a point in diastole corresponding to 80% of the RR interval. Patients held their breath during the entire 20-level acquisition. Positioning was checked after image acquisition, and additional slices were obtained if necessary. Total procedure time including positioning and setup was <10 minutes. Radiation exposure was <12 mGy, comparable to 1 abdominal x-ray.

Image analysis and quantification: The number of calcific deposits identified, and their area, volume and total calcium score were determined for each study. A calcific deposit was considered present on a level if contiguous pixels with a computed tomographic number of >130 Hounsfield units (HU) had an area of >0.51 mm^2. Adjacent areas of calcium seen on contiguous levels were counted as separate lesions although they may have represented single large lesions, as was confirmed on some 3-dimensional reconstructions. Calcific deposit volume was calculated by multiplying the lesion area by the slice thickness (3 mm) and expressed in cubic millimeters. Total calcific deposit volume was the sum of all identified lesion volumes.

The calcium score for each deposit was calculated by multiplying its area in mm^2 by a density score. The density score was determined by the peak CT number of the lesion as follows: 1 for a peak CT number of 130 to 199 HU, 2 for 200 to 299 HU, 3 for 300 to 399 HU and 4 for >400 HU. The total calcium score was the sum of the individual lesion scores. The mean CT num-

TABLE II Changes in Calcified Plaque Area, Volume and Computed Tomography Number Seen By Ultrafast Computed Tomography

Pt. No.	Area 1 (mm^2)	Area 2 (mm^2)	Change in PV (mm^3)	Mean CT# 1 (HU)	Mean CT# 2 (HU)	%Change (CT#)	TCS 1	TCS 2
				Group II				
6	55.64	64.94	27.90	378	492	30	192	237
7	47.91	47.62	−0.87	276	266	−4%	137	106
8	5.15	7.22	6.21	291	480	65%	10	28
9	5.41	8.76	10.05	221	262	19%	10	18
10	6.95	15.70	26.25	180	254	42%	11	37
11	13.4	18.17	14.31	316	300	−5%	41	59
12	31.69	35.80	12.33	260	273	5%	104	115
13	19.82	38.89	57.21	224	363	62%	53	115
14	84.01	104.39	61.14	330	405	23%	343	377
15	0.51	3.34	8.49	162	210	30%	2	11
Mean	27.05	34.48	22.30	264	331	27%	90	110
SD	±27	±31	±21	±68	±99	±25	±104	±110
				Group III				
16	147.13	199.26	156.39	503	551	10%	560	708
17	21.64	39.84	54.60	205	270	32%	50	93
18	147.64	203.10	166.38	289	352	22%	422	691
19	85.26	153.94	206.04	230	249	8%	177	321
20	48.66	98.89	150.69	220	228	4%	120	211
21	43.25	72.22	86.91	212	285	34%	91	216
22	145.67	200.55	164.64	305	386	26%	481	694
23	189.16	288.40	297.72	267	319	19%	560	956
24	121.39	162.61	123.66	359	345	−4%	437	539
25	70.07	91.74	65.01	237	289	22%	157	212
Mean	101.99	151.06	147.20	283	327	17%	305	464
SD	±55	±75	±71	±91	±93	±12	±194	±276

1 = study one; 2 = study two; area = total calcified plaque area; CT# = computed tomography number; HU = Hounsfield units; PV = calcified plaque volume; SD = standard deviation; TCS = total calcium score.

ber of blood in the aortic root was checked on each study to detect any drift in CT numbers over time. No systemic change was seen.

To ensure that changes in the parameters measured were not due to differences in the region of the heart scanned, all studies were reviewed to determine at what level the left coronary artery was first seen. With use of that level as a baseline, an equal number of levels from each study was used to compare results between the 2 studies. Two patient studies had obvious duplication of levels or skipped areas due to motion and were excluded from analysis.

In addition to looking at the changes in total calcified plaque volume and area, calcium score and number of calcific lesions, comparable levels from the 2 serial studies were examined side by side on the computer console. Each lesion identified on the first study was matched, if possible, to the corresponding lesion on the second study. New lesions on the second study and old lesions not seen on the second study were identified. If a new calcific lesion was seen on the second study the same area was examined on the first study to see if a subthreshold lesion (lesion with peak CT of >100 but <130 HU or peak CT >130 but with an area of <0.51 mm^2) could be identified.

Three-dimensional reconstructions: Three-dimensional reconstructions were produced from the original 20-slice data sets using a commercially available work station (Dimensional Medicine, Inc.). A surface map of the heart was reconstructed. The coronary arteries were identified and areas with a CT of >130 HU were color-coded or highlighted in the 3-dimensional reconstruction. The volume of calcified plaque was quantified by measuring the number of voxels with a CT number of >130 HU, excluding lesions of <0.51 mm^2 on individual slices. Volumes were calculated in cubic centimeters. Once the 3-dimensional images were obtained they could be easily viewed from any perspective by computer manipulation.

Statistical methods: This study was a 2-factor experiment with the presence or absence of obstructive CAD as the first factor and study year (first or second study) as the second factor. The effect of these factors on total calcium score, mean CT number, calcified plaque area and calcified plaque volume were evaluated. The subjects were considered to define a third factor, the "subject factor," which was crossed with the disease factor and nested under the year factor. A linear model was used for each of the dependent variables considered in the study.

To satisfy the homogeneity assumptions of the sources of variations of the experimental data, statistical analyses were performed on the log transformed total calcium score, mean CT number, total calcified plaque area and total calcified plaque volume. Accordingly, the transformed data were analyzed as an analy-

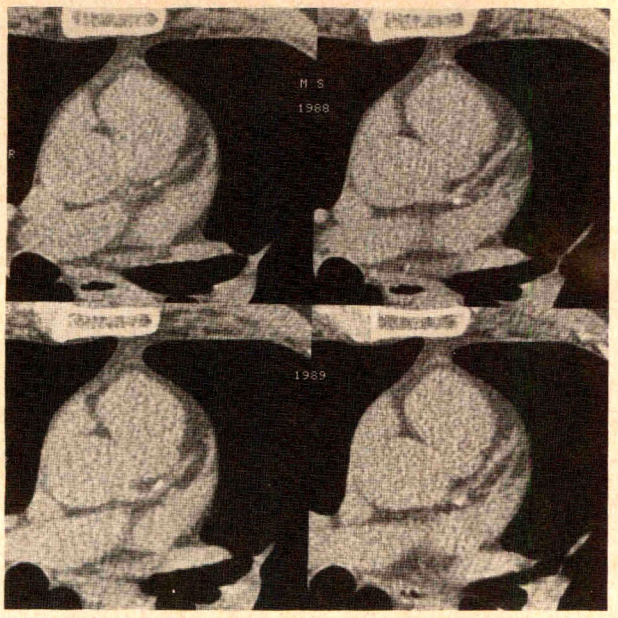


FIGURE 1. Calcific deposits, which are white compared with the rest of the vessel, are seen in the proximal left anterior descending *(top left)* and proximal circumflex arteries *(top right)* in the first study in 1988. Comparable levels from the second study in 1989 *(bottom left and right)* show the same 2 deposits with an increase in area and density (peak CT numbers) compared with the first study.

sis of variance, 2-factor factorial with repeated measures on 1 factor.[15]

RESULTS

Group I: All 5 patients without calcium on the first study showed no calcium on the second study.

Groups II and III: Results are summarized in Tables I and II. Nineteen of 20 patients with calcium on the first study showed an increase in total calcified plaque area and volume and total calcium score. There were statistically significant differences in mean total calcium score, total calcified plaque volume and total calcified plaque area between groups II and III in both years ($p = 0.0006$, $p = 0.0021$, $p = 0.0007$, respectively). No significant difference was seen between the 2 groups in average peak CT number. There were significant increases in average peak CT number, total calcified plaque volume and area and total calcium score in both groups between the first and second studies ($p < 0.0001$ for all).

Most calcific deposits showed an increase in area and peak CT number in the second study (Figure 1). For the total group of 20 patients with calcified lesions there was an increase in mean total calcified plaque volume of 44% and an increase in mean peak CT number of 20%. The mean total calcified plaque volume increased by 27% in group II and 48% in group III, although the baseline level of calcium was significantly higher in group III (mean total plaque volume of 81.2 ± 82.5 mm^3 in group II vs 306 ± 167.5 mm^3 in group III on the first study) (Figure 2).

The total number of calcific lesions increased in both groups II and III (Table I), but the change in number of calcific deposits did not accurately reflect the number of new deposits identified, because small adjacent deposits tended to coalesce to form larger single deposits in the follow-up study (Figure 3). The number of calcific deposits also could differ in the 2 studies owing to slight changes in positioning that caused a lesion to be seen on a different number of levels. Thus, the calcific deposit number could decrease or stay constant despite the presence of new lesions, or could increase without any new lesions being present. Therefore, the calcific deposit number was not a good indicator of progression or regression of calcium in the planar reconstructions.

Reproducibility: In the side-by-side comparison of individual lesions, 235 of 241 deposits (98%) identified on the first study could be accounted for on the second study as distinct individual deposits or as having coalesced into a larger calcific deposit. Owing to the slight changes in positioning between the 2 studies, this comparison was time consuming and tedious when large calcific deposits were present. However, there was remarkable similarity of comparable levels in most patients (Figure 4).

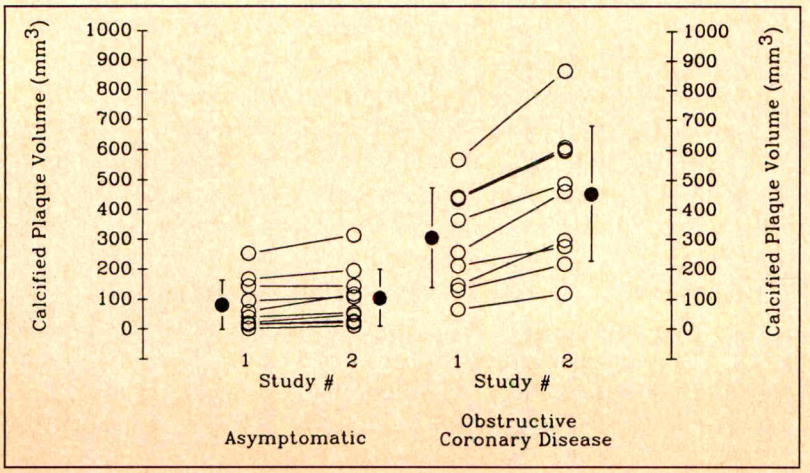


FIGURE 2. Changes in calcified plaque volume between the 2 studies are compared in asymptomatic subjects and patients with obstructive coronary artery disease. Initial and follow-up mean calcified plaque volumes were significantly higher in the group with obstructive coronary artery disease ($p < 0.001$). Both groups had significant increases in mean calcified plaque volume in the second study ($p < 0.001$).

Three-dimensional reconstructions: Three-dimensional images were obtained in 4 patients (Figure 5). The 3-dimensional images eliminated the problem of evaluating large lesions seen on >1 level because they could be clearly identified as single lesions on the 3-dimensional reconstructions. This eliminated the problem of calcific lesion number previously discussed. They also eliminated problems associated with changes in positioning between the 2 studies. Data from the entire 20-slice study are presented in 1 composite image, allowing study comparison by looking at 2 instead of 40 images. Computer manipulation allows the images to be viewed from any perspective. Patient motion during acquisition is easily identified on the 3-dimensional images, preventing errors in measurement of calcified plaque volume. Identification of new deposits is also facilitated.

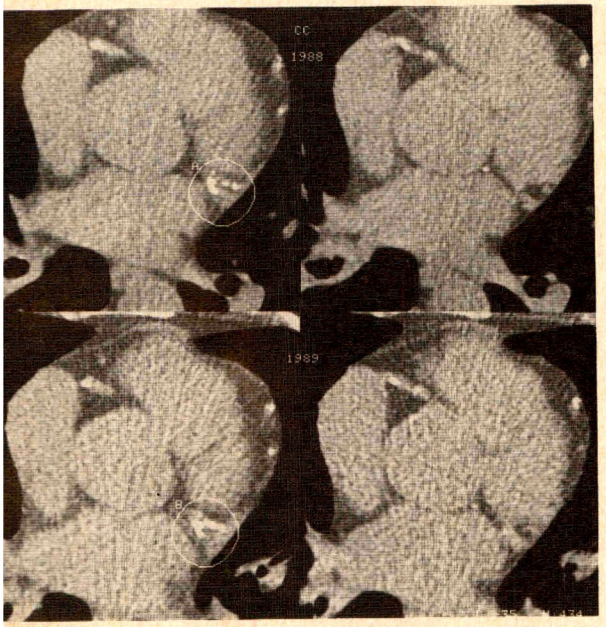


FIGURE 3. Coalescence of calcific deposits is demonstrated in this subject. Calcium in the circumflex and marginal arteries in circle A, *top left,* are shown to have coalesced into a single large deposit in circle B, *bottom left,* 1 year later. Also note excellent reproducibility of other calcific deposits in the left anterior descending and right coronary arteries between the 2 studies.

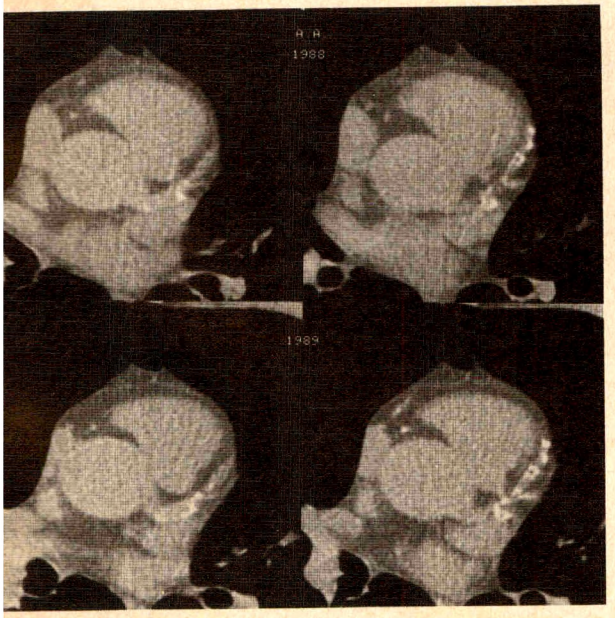


FIGURE 4. Comparable levels in the serial studies show excellent reproducibility even in the presence of extensive calcified plaque in the left anterior descending artery *(top and bottom right).*

New calcific deposits: Six of 10 subjects in group II had 18 new calcific deposits compared with 55 new deposits in 9 of 10 subjects in group III ($p = 0.058$, Table I). New deposits were small in area and low in density, with a mean area of 2.41 ± 2.33 mm^2 and a mean CT number of 179 HU in group II and 199 HU in group III. In 26 (36%) of the new lesions, a subthreshold lesion could be identified on the initial study.

DISCUSSION

Serial ultrafast CT studies demonstrated the potential to track calcific deposits over time. Ninety-eight percent of calcific deposits seen in the first study were accounted for in the second study. Calcific deposits may not be seen for 2 reasons (disregarding possible regression of calcified lesions). First, patient motion in either the first or second study may lead to a deposit being absent or counted twice due to redundant or skipped levels. Second, volume-averaging could result in small calcific deposits being subthreshold in 1 study

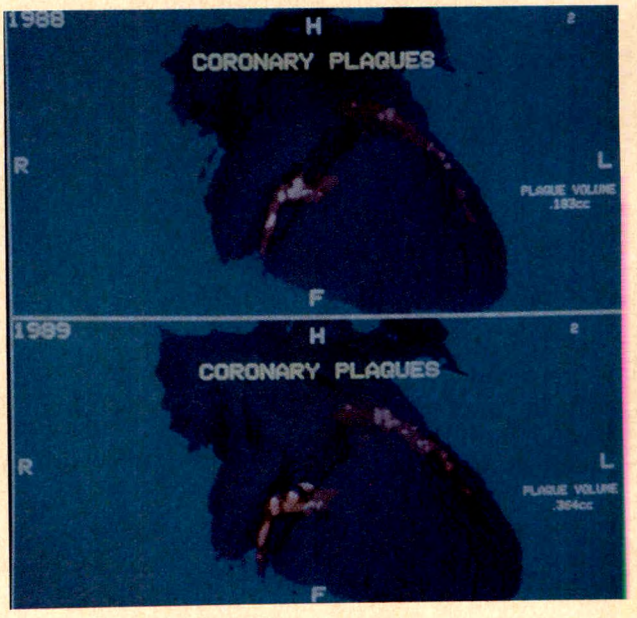


FIGURE 5. Three-dimensional reconstructions of serial studies permit the data from each 20-slice study to be presented in 1 image, greatly facilitating study comparison. Increase in calcified plaque volume of individual calcific deposits is readily identified. Calcific deposits, which on planar images would be seen on multiple slices, can be seen as single large lesions. These color-coded images show extensive coronary calcium in both the right and left coronary arteries with an increase in calcified plaque volume that is easily seen.

depending on the location of the lesion with respect to the imaging plane. Because nearly all calcific deposits were accounted for, these do not appear to be important obstacles for following the progression of disease.

Three-dimensional reconstruction of the coronary anatomy may be the best method for comparing serial studies because it compensates for changes in lesion configuration due to changes in positioning or volume averaging. Patient motion is easily identified, and new, small lesions can be seen without the need for sometimes tedious, side-by-side comparison of planar images.

The findings of this study show a substantial increase in calcified plaque volume between the 2 CT examinations (27% for those without and 48% for those with established CAD). These results are, if anything, biased against the asymptomatic group because some patients in group II, not studied angiographically, may have had obstructive disease that was not clinically manifest. This would tend to diminish any difference between the 2 groups. Since the mean peak CT number of calcified lesions is well below the maximal CT number that the scanner is capable of measuring (1,047 HU), increases of this magnitude can be followed for many years.

Besides showing a greater increase in the amount of calcium, the obstructive CAD group showed a larger number of new calcific deposits, although the difference just missed being statistically significant ($p = 0.058$). New areas of calcified plaque tended to be small, with CT numbers <200 HU. In approximately one-third of these calcific deposits, a subthreshold lesion was present on the previous study. This raises the possibility that our threshold for calcium may be set too high. This was initially done deliberately to make the identification of calcium more certain and less likely to result in a false-positive study. Long-term follow-up in a larger group of patients may lead to selection of a lower threshold value for calcium if subthreshold calcific deposits consistently show progression to above-threshold lesions.

From the aforementioned discussion it appears that the "age" of calcific deposits is related to the density of the calcified lesion. Calcific deposits with CT numbers <200 would be the most recently formed and are most likely to be affected by any change in the rate of calcified plaque formation.

The group of patients with no calcium on the first study showed no evidence of calcium on the second study. Our previous work would suggest that this group would have an extremely low prevalence of ischemic heart disease.[14] A longer follow-up period in a larger group of subjects without calcium would be valuable to determine the ultimate prognostic value of this finding.

This study supports the potential of ultrafast CT to detect and follow the progression of coronary atherosclerosis in both asymptomatic persons and those with known obstructive CAD. Whether interventional therapy can decrease the size of lesions that are already calcified or stop the increase in size and density of preexisting calcific deposits is uncertain. One subject in this study had a slight decrease in total calcium score and plaque volume that could only be accounted for by a decrease in calcified plaque. This subject, a 48-year-old physician, had a decrease in total serum cholesterol from 260 to 150 mg% by a strict diet and drug therapy. Future studies will determine the value of ultrafast CT for following the effects of interventions on the rate of progression of coronary atherosclerosis.

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Evolution of Myocardial Ischemia and Left Ventricular Function in Patients With Angina Pectoris Without Myocardial Infarction and Total Occlusion of the Left Anterior Descending Coronary Artery and Collaterals from Other Coronary Arteries

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Repeated episodes of myocardial ischemia might lead to progressive impairment of left ventricular (LV) function. This radionuclide study assessed myocardial ischemia and LV function several years after documented coronary occlusion without myocardial infarction. Over 5 years, 24 consecutive patients, who underwent cardiac catheterization for angina pectoris without myocardial infarction, had isolated total occlusion of the left anterior descending coronary artery with well-developed collateral vessels. Five patients were successfully treated by coronary bypass grafting and 3 by coronary angioplasty. Among the 16 medically treated patients, 1 was lost to follow-up and 1 died (extracardiac death). The mean (± standard deviation) follow-up (14 patients) was 48 ± 15 months. At follow-up, 8 patients still had clinical chest pain, 11 received antianginal therapy, 4 patients had no stress ischemia and the other 10 had ≥1 sign of stress ischemia. All patients had a normal LV ejection fraction at rest (mean 60 ± 3%; range 55 to 65%). Collateral circulation preserves LV function at the time of occlusion and, in some cases, prevents the development of myocardial ischemia; in patients with persisting myocardial ischemia after well-collateralized coronary occlusion, LV function is not impaired at long-term follow-up.

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Controversy exists concerning the effectiveness of coronary collateral vessels in humans.[1–4] Development of collateral circulation seems to limit myocardial damage in some cases of coronary obstruction.[5–7] In the presence of total occlusion of the left anterior descending coronary artery, the anterior territory might not be completely protected from ischemia by well-developed collateral vessels[8] and might present severe myocardial asynergy during stress.[9] Chronic myocardial ischemia itself could influence prognosis[10] and alter left ventricular (LV) function.[11–14] We studied a highly selected population of patients with coronary occlusion and preserved LV ejection fraction as a model of possible long-standing repeated myocardial ischemia without interference of prior infarction or risk of subsequent infarction. The patients were followed up for several years to determine by radionuclide studies (1) if myocardial ischemia persisted at long-term follow-up, and (2) what the status of LV function was after several years of persisting LV ischemia.

METHODS

Study patients: Among 7,871 patients who underwent cardiac catheterization from January 1983 to December 1987, a consecutive series of 24 patients, who underwent their initial coronary angiography at our institution for angina pectoris without prior myocardial infarction, were selected because of the presence of a complete, isolated occlusion of the left anterior descending coronary artery with collateral vessels from other coronary arteries. Coronary angiography was justified in all patients by the existence of clinical ischemic symptoms without criteria of prior myocardial infarction. Among the 24 patients, 5 were treated surgically and 3 underwent percutaneous recanalization with success. These 8 were excluded from the study. Thus, the study population comprised 16 medically treated patients (14 men, 2 women). All patients were followed

up until December 1989, when the patients gave informed consent to undergo stress radionuclide studies. Treated patients had to stop their antianginal medications 2 days before the stress tests.

Initial cardiac catheterization: Left ventriculography was routinely performed in the 30° right anterior oblique and the 50° left anterior oblique projections. Calculation of LV ejection fraction was based on the area-length method.[15] Eight LV segments (4 anterior segments—septal, anterobasal, anterolateral and apical) were identified in both projections. The extent of irreversible myocardial damage was assessed according to American Heart Association criteria.[16] Each segment was subjected to a 5-point scoring system: 1 = normal, 2 = moderate hypokinesia, 3 = severe hypokinesia, 4 = akinesia and 5 = dyskinesia. The individual regional wall motion score reflecting severity and extent of damage was determined by 2 independent observers. Collateral vessels, visualized by selective coronary angiography with 7Fr catheters, were scored by 2 independent observers according to the degree of opacification of the native vessel distal to its occlusion. Collateral vessels were assigned a numeric score between 0 and 3 according to the criteria of Cohen and Rentrop[17]: grade 0 = no visible filling of any collateral channels, grade 1 = filling of side branches of the artery to be perfused via collateral vessels without visualization of the epicardial segment, grade 2 = partial filling of the epicardial segment by collateral vessels, and grade 3 = complete filling of the epicardial segment by collateral vessels. When the degree of opacification varied in a given patient, the score corresponding to the best visualization of the distal vessel was used. In patients in whom the distal segment of the occluded vessel filled from both right and left coronary collateral vessels, the sum of the score (not to exceed 3) was used.

Stress test protocol: Before stress tests were performed, medications were confirmed to have been stopped for ≥2 days and a baseline electrocardiogram was recorded. Upright cycloergometer testing for exercise thallium-201 tomography and supine cycloergometer testing for stress radionuclide LV ejection fraction were performed with 12-lead electrocardiographic monitoring at each minute of exercise and with continuous monitoring of leads V_1, V_5 and aVF. The protocol began at 40 W and increased by increments of 30 W every 3 minutes. Exercise end points were physical exhaustion, development of angina pectoris, sustained ventricular tachyarrhythmia or exertional hypotension. The stress electrocardiogram was considered positive if there was >2 mm of ST-segment depression occurring at 0.08 second after the J point on any of the surface electrocardiographic leads.

Thallium-201 imaging: At near maximal exercise, 1 mCi of thallium-201 per 25 kg body weight (without exceeding 3 mCi) was injected intravenously, and exercise was continued for an additional minute. The patients were imaged 10 minutes after stress; redistribution imaging was performed 4 hours later and a second dose of 30% of the initially injected total dose of thallium-201 was reinjected to enhance detection of ischemic viable myocardium.[18] Tomographic acquisition was performed using a rotating gamma camera equipped with a low-energy, general purpose, parallel hole collimator interfaced with a computer system (Sopha-Medical). In a 180° arc rotation—from a 30° left posterior oblique to a 30° right anterior oblique projection around the craniocaudal axis of the patient—32 projections were obtained for 30 seconds each in a 64 × 64 matrix. After reconstruction, data were reorganized to contiguous short-axis, vertical long-axis and horizontal long-axis slices (8-mm thick) encompassing the left ventricle.

Analysis of thallium-201 tomograms: Stress and rest thallium-201 myocardial tomograms were divided into 20 sectors for each patient and assigned on 5 spaced regions. The anterior, septal, inferior and lateral regions were analyzed in the apical, midventricular and basal slices of the short-axis views; 2 apical sectors were studied on the midvertical long-axis slice.[19] All tomographic images were scored by 2 experienced observers using a 4-point scoring system: 0 = normal, 1 = equivocal, 2 = moderate, and 3 = severe reduction of thallium-201 uptake. A perfusion defect was considered present when a myocardial segment had an initial post-stress score ≥2. Stress defects with a visual score <2 at 4-hour imaging were called "reversible," and defects with a score ≥2 were termed "nonreversible."[20]

Radionuclide left ventricular ejection fraction: Multigated equilibrium radionuclide studies were performed in the supine position using previously described techniques.[21] A dose of 20 mCi of technetium-99m pertechnetate was injected intravenously. The cardiac blood pool was imaged with a single crystal gamma camera interfaced with a computer system (Sopha-Medical). The camera head was oriented to maximize ventricular separation, usually with a 30° to 60° left anterior oblique orientation. The cardiac blood pool was imaged for 5 minutes at rest and during the last 2 minutes of the maximal exercise level, and 16 frames were obtained from the cardiac cycle.

Analysis of data of radionuclide studies: Radionuclide LV ejection fraction was determined according to the following formula: (EDC − BC) − (ESC − BC)/(EDC − BC), where EDC is end-diastolic counts, ESC is end-systolic counts and BC is background counts.

TABLE I Clinical Individual Data at Study Entry (Before Catheterization) and at Follow Up

Pt.	Sex & Age (yr)	Duration of AP (mos) Before Cath.	Initial Radionuclide LVEF	F/U (mos)	Canadian Functional Class at F/U	No. of Antianginal Medications at F/U
1	F57	3	—	78	Atyp.	2
2	M63	48	—	67	Atyp.	2
3	M59	19	64	65	I	2
4	M58	12	—	64	0	0
5	M65	3	60	57	0	1
6	M54	7	—	47	0	0
7	M55	1.5	66	46	II	2
8	M54	108	56	42	I	2
9	M62	12	—	39	Atyp.	2
10	M47	12	—	39	II	3
11	M63	36	55	38	II	3
12	M66	24	—	33	0	2
13	M58	96	60	32	0	2
14	M60	0.5	62	32	0	0

AP = angina pectoris; Atyp. = atypical chest pain; Canadian funct. class = Canadian functional class of angina pectoris; Cath = catheterization; F/U = follow-up; LVEF = left ventricular ejection fraction.

Regions of interest and the background region were obtained by using hand-drawn regions. Hand-drawn ejection fraction determinations were performed by 2 independent observers who were blinded to each other's results as well as to initial cineangiographic results.

Statistical analysis: All values are presented as mean ± standard deviation. Statistical analysis used Student's paired *t* test for comparing radionuclide rest LV ejection fraction at baseline and follow-up. A p value <0.05 was considered statistically significant.

RESULTS

Initial clinical and hemodynamic data (Tables I and II): One man was lost at follow-up (6.2%) and 1 woman died of an extracardiac cause (complicated systemic lupus erythematosus). The mean age of the other 14 patients was 59 ± 5 years at study entry. The mean duration of anginal symptoms was 27 ± 34 months. Electrocardiographic analysis showed poor R-wave progression in leads V_1 and V_2 in only 2 patients and isolated negative T waves in the anterior leads in 3 other patients. Except for the left anterior descending coronary occlusion, no patient had ≥50% stenosis in any of the other coronary vessels. Angiographic collateral circulation was well developed in all patients. Mean cineangiographic LV ejection fraction was normal (65 ± 6%).

Follow-up and isotopic data (Tables I and III): The mean follow-up period was 48 ± 15 months. At follow-up, 8 patients still had clinical chest pain. No Q waves were present on the rest electrocardiogram. All but 3 patients, however, were treated with antianginal medications. The exercise test was negative in 10 patients. However, thallium-201 tomography was normal in only 5 patients; it detected a moderate reversible anteroapical defect in 7 patients and a mild persistent apical defect in 2 other patients. The other wall segments were normal, except in 3 patients with inferior wall abnormalities: 2 equivocal reversible perfusion defects considered to be nonsignificant (patients 9 and 13) and 1 mild persistent perfusion defect (patient 7). For technical reasons, radionuclide LV ejection fractions in 2 patients could not be determined at stress. All patients had a normal LV ejection fraction at rest (mean 60 ± 3%) as well as a normal stress LV ejection fraction (mean 61 ± 5%). Resting regional wall motion was normal in all but 3 patients (patients 3, 5 and 12) with moderate anteroseptal hypokinesia without compensatory increase in wall motion in nonischemic regions. No difference was seen in resting regional wall motion between

TABLE II Individual Data of Coronary Angiography and Left Ventriculography at Study Entry

Pt.	LAD Segment	Collateral Grading	No. of Diseased LA Wall Segments (max:4)	LA Wall Motion Score (min:4–max:20)	LVEF (%)
1	Distal	2	2	9	61
2	Mid	2	0	4	55
3	Proximal	2	2	7	73
4	Proximal	2	1	6	59
5	Mid	3	2	9	63
6	Distal	2	1	5	60
7	Mid	3	0	4	73
8	Proximal	2	0	4	73
9	Mid	3	0	4	69
10	Distal	3	1	5	62
11	Proximal	3	0	4	71
12	Mid	3	1	5	68
13	Mid	3	0	4	63
14	Proximal	3	1	7	63

LA = left anterior; LAD = left anterior descending coronary artery; max = maximal; min = minimal; other abbreviations as in Table I.

TABLE III Individual Data of Exercise Thallium-201 Tomography and Rest and Stress Radionuclide Left Ventricular Ejection Fraction

Pt.	Stress Test			No. of LA Wall Segments with Stress Defects (max:8)	Stress Defects Score	Reversibility (%)	LVEF (%)	
	%Th Max HR	Pain	ECG				Rest	Stress
1	91	0	0	0	0	—	61	64
2	75	0	0	1	2	100	58	—
3	75	0	0	0	0	—	61	65
4	87	0	0	0	0	—	61	58
5	100	0	0	0	0	—	56	60
6	96	0	0	1	3	100	61	67
7	77	+	+	2	3	100	65	59
8	77	+	+	1	2	100	63	57
9	100	0	0	1	2	100	62	57
10	78	+	+	4	3	50	61	57
11	67	+	+	3	2	100	60	—
12	66	0	0	1	3	0	57	57
13	97	0	0	3	3	100	55	60
14	75	0	0	0	0	—	60	74

ECG = electrocardiogram; %ThmaxHr = % of theoretical maximal heart rate; + = positive; 0 = negative; — = absent; other abbreviations as in Tables I and II.

baseline and follow-up in the 7 patients who had 2 radionuclide studies. However, 6 patients (patients 4, 7, 8, 9, 10 and 12) had an abnormal ejection fraction response to exercise. On the whole, at follow-up, 4 patients (patients 1, 3, 5 and 14) had no stress ischemia, showing that collateral circulation was thus sufficient to protect myocardium in some cases. However, 2 patients achieved only 75% of maximal predicted heart rate: in these 2, absence of ischemia might be related to submaximal stress. On the other hand, the other 10 patients had at least 1 sign of stress ischemia and their rest LV ejection fraction at follow-up remained normal. Three of these (patients 7, 8 and 11) were of particular interest: at follow-up, all 3 had unequivocal signs of persisting myocardial ischemia, although rest LV ejection fraction remained unchanged when compared with its baseline radionuclide value.

DISCUSSION

It has been suggested that repeated myocardial ischemia could progressively produce alteration of LV function[11,12,14] and should be treated.[22] To obtain a possible model of long-standing repeated myocardial ischemia without the risk of occurrence of subsequent myocardial infarction, we selected patients with isolated total left anterior descending coronary occlusion, who had not developed myocardial infarction at the time of occlusion, and who did not risk developing myocardial infarction in the future, as the coronary artery was already totally occluded and well collateralized.[5] Our aim was (1) to confirm the persistence of ischemia in the anterior territory, and (2) to assess the long-term influence of such persisting ischemia on LV ejection fraction.

Persistence of long-standing repeated myocardial ischemia: Although angiographic assessment of collateral circulation remains an imperfect measurement of its functional significance,[23] all our patients had well-developed collateral vessels, demonstrated by satisfactory filling of the epicardial segment of the occluded artery. Well-developed collateral vessels initially avoided the constitution of myocardial infarction at the time of occlusion with preserved LV ejection fraction, as suggested previously.[5–7] The long duration of preceding angina pectoris could also have played an important role in the development of this collateral circulation.[5] However, it has been demonstrated by exercise thallium-201 tomography[24] that well-developed collateral vessels could provide at least relative protection from stress-induced ischemia.[25–27] Our study showed that the functional significance of well-developed collateral vessels was different according to the patients, despite a similar angiographic appearance. Some patients still had angina pectoris; reversible myocardial defects were found in all symptomatic patients except 1, and also in 3 asymptomatic patients, testifying to the existence of silent ischemia.[28] On the other hand, 4 patients had no stress ischemia. It thus appears that in some patients, collateral circulation can sufficiently protect the myocardium to avoid episodes of ischemia. In addition, it is likely that the present study did not include a certain number of patients protected by such well-developed collateral vessels who therefore did not seek medical attention.

Preservation of left ventricular function at long-term follow-up: Myocardial ischemia can induce LV dysfunction at rest[13,29,30] and at exercise.[31–33] However, LV function is less altered when well-collateralized occlusions exist.[9] On the other hand, well-developed col-

ıteral vessels to a completely occluded artery seem to revent severe asynergy at rest but not during stress.[8,9] Moreover, repeated episodes of ischemia might lead to lteration of LV function.[11,12,14] In our study, 10 pa-ents had persisting stress-induced ischemia at long-erm follow-up. In these patients with initially normal .V function, there was no subsequent alteration of LV jection fraction at follow-up. Therefore, well-developed oronary collateral vessels preserved LV ejection frac-ion both at the time of coronary occlusion and at long-erm follow-up, despite the persistence of clinical isch-:mia; however, in 4 of the patients who were asymp-omatic with medical therapy, antianginal treatment night have played a favorable role in reducing the isch-:mic burden of the left ventricle.

Study limitations: One limitation of this study was he small number of patients included. However, the :eries was consecutive over 5 years and the small group of patients was due to the fact that a left anterior de-scending coronary occlusion without myocardial infarc-tion was not commonplace and was often treated non-medically. A second potential limitation was the ab-sence of baseline radionuclide LV ejection fraction in 50% of the patients. All patients had a normal baseline angiographic LV ejection fraction, which could not be compared with radionuclide LV ejection fraction at fol-low-up. However, radionuclide rest LV ejection frac-tions of the 7 patients with values at baseline and at follow-up were not significantly different. A third limi-tation was related to the absence of coronary angiogra-phy at follow-up to detect spontaneous recanalization of the left anterior descending coronary artery or progres-sion of coronary artery disease on the other coronary arteries.[25,34] Spontaneous recanalization seems unlikely because all but 2 patients had had symptoms for ≥3 months before the initial coronary angiography. More-over, progression of the disease on the collateral vessels should be detected by exercise thallium-201 tomogra-phy revealing perfusion defects in regions other than the anterior territory, and only 3 patients presented with equivocal or mild inferior wall defects.

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Usefulness of Early Versus Late Programmed Ventricular Stimulation in Acute Myocardial Infarction

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To determine the influence of timing on the prognostic value of programmed ventricular stimulation after acute myocardial infarction (AMI), 32 patients were studied on day 19 (early study) and again on day 36 (late study) after AMI using up to 3 extrastimuli. At the early study, sustained monomorphic ventricular tachycardia (VT) was induced in 12 patients (38%), sustained polymorphic VT in 8 (25%), nonsustained monomorphic VT in 1 (3%), nonsustained polymorphic VT in 1 (3%) and no inducible arrhythmia in 10 (31%). At the late study, sustained monomorphic VT, nonsustained monomorphic VT and nonsustained polymorphic VT were induced in 8 patients (25%) each, and no inducible arrhythmia in 8 (25%). Of the 12 patients who had inducible sustained monomorphic VT at the early study, 7 had noninducibility of sustained monomorphic VT at the late study. Of the 20 patients who had noninducibility of sustained monomorphic VT at the early study, 3 had inducible sustained monomorphic VT at the late study. During the follow-up period (mean ± standard deviation 21 ± 8 months), there were 2 sudden cardiac deaths and 3 occurrences of sustained VT. Univariate analysis revealed both inducibilities of sustained monomorphic VT at the early study ($p = 0.045$) and at the late study ($p < 0.001$) to be predictive of sudden cardiac death or clinical occurrence of sustained VT. However, inducibility of sustained monomorphic VT at the late study had a higher sensitivity (100%), specificity (89%), positive predictive value (63%) and negative predictive value (100%) than at the early study (80, 70, 33 and 95%, respectively). These data suggest that the timing of programmed stimulation study after AMI influences the inducibility of VT and its predictive ability. Programmed ventricular stimulation after AMI may need to be done at least 1 month after AMI for optimal value.

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Programmed ventricular stimulation in patients with documented sustained ventricular tachycardia (VT) has been used to evaluate the efficacy of antiarrhythmic therapy. However, the role of programmed ventricular stimulation in patients after acute myocardial infarction (AMI) without documented spontaneous sustained ventricular tachyarrhythmias has been the subject of much debate.[1–11] One source of potential difficulty may be due to the timing of the programmed ventricular stimulation after AMI. The purpose of this study was to determine the influence of timing on the prognostic value of programmed ventricular stimulation after AMI.

METHODS

Study patients: The study group consisted of 50 consecutive patients <75 years old admitted to Tsuchiura Kyodo General Hospital and Musashino Red Cross Hospital between January 1987 and December 1987 because of Q-wave AMI. Patients were excluded from the study if they had 1 of the following: uncontrolled angina or heart failure, sustained VT or fibrillation, or significant nonischemic heart disease. Of the 50 patients, 6 died before the first study on day 19, 10 were excluded by study criteria and 2 refused to participate. Thirty-two patients gave written informed consent to undergo programmed ventricular stimulation. Clinical characteristics of the 32 patients are summarized in Table I.

Our group recently reported results on 133 survivors of AMI who underwent programmed stimulation at a mean of 1.8 months after AMI.[8] The present study is independent and no patient in the current study was included in the previous reports. The study protocol was approved by the Institutional Review Board of our hospitals.

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TABLE I Clinical Characteristics

No. of patients	32
Clinical profile	
M/F	24/8
Mean age (yrs)	61 ± 10
Age range (yrs)	43–75
Location of infarction	
Anterior	22 (69%)
Others	10 (31%)
Peak CK (IU/liter)	1,530 ± 1,177
Percutaneous transluminal coronary recanalization	5 (16%)
Angiography	
No. of diseased vessels	1.9 ± 0.9
LV aneurysm	8 (25%)
Ejection fraction (%)	41 ± 19
Cardiac index (liters/min/m^2)	2.7 ± 0.6
LV end-diastolic pressure (mm Hg)	22 ± 6
Treatment during follow-up	
Beta-blocking drugs	9 (28%)
PTCA	1 (3%)
Coronary artery bypass graft	0 (0%)
Mean follow-up period (mos)	
All patients (n = 32)	21 ± 8
Range	3–33
Survivors (n = 29)	22 ± 6

CK = creatine kinase; LV = left ventricular; PTCA = percutaneous transluminal coronary angioplasty.

Programmed stimulation: Programmed ventricular stimulation was performed on day 19 ± 3 and on day 36 ± 4 after AMI. No study patients received β blockers or other antiarrhythmic therapy for ≥7 days before study. Quadripolar electrode catheters were inserted percutaneously and positioned at the right ventricular apex and outflow tract. Stimulation was performed with a programmable stimulator. Stimuli, with rectangular pulses 1.0 ms in duration at twice the diastolic threshold, were introduced from the right ventricular apex and outflow tract. The following protocol was used: (1) A single ventricular extrastimulus (S2) was introduced in late diastole during 2 paced ventricular cycle lengths (S1–S1 = 600 and 400 ms) and moved earlier until ventricular refractoriness was encountered. (2) Double ventricular extrastimuli were then introduced starting at an S1–S2 interval 50 ms longer than the ventricular refractory period and at an S2–S3 interval that was equal to S1–S2. S2–S3 was shortened until S3 failed to capture the ventricle and S1–S2 was then shortened until S3 evoked a response. This was continued until both S2 and S3 reached refractoriness. (3) A third extrastimulus (S4) was delivered in an analogous fashion during 2 paced ventricular cycle lengths. The end point of the study was either the initiation of a sustained VT or ventricular fibrillation.

The following definitions were used: (1) Sustained monomorphic VT denoted repetitive ventricular response with uniform QRS configuration lasting ≥30 seconds or requiring termination before 30 seconds because of hemodynamic compromise. (2) Sustained polymorphic VT denoted repetitive ventricular response with nonuniform QRS configuration lasting ≥30 seconds or requiring termination before 30 seconds because of hemodynamic compromise. Ventricular fibrillation was classified as sustained polymorphic VT. (3) Nonsustained VT denoted a series of ≥5 repetitive ventricular responses, terminating spontaneously in <30 seconds. (4) No inducible arrhythmia denoted ≤4 repetitive ventricular responses. Reproducibility of induced sustained arrhythmias was not checked in this study.

Holter monitoring: Ambulatory electrography (24-hour Holter monitoring) was performed on day 19 ± 3 and on day 36 ± 4 after AMI ≥7 days after antiarrhythmic medication had been discontinued. Ventricular arrhythmias were classified according to the method of Lown and Wolf,[12] but grade 5 was excluded.

Clinical and hemodynamic data: Various clinical and hemodynamic data were assessed. All patients underwent complete catheterization with coronary angiography and left ventriculography between the nineteenth and thirty-sixth day after AMI. Significant coronary lesions were defined as ≥60% reduction of luminal diameter. The presence of ventricular aneurysm was determined angiographically according to criteria of the Coronary Artery Surgery Study.[13] Left ventricular ejection fraction was determined from ventriculography.[14]

Treatment: As part of the study design, no patients were treated with antiarrhythmic drugs. Nine patients were treated with β blockers to control their angina. No patient underwent coronary artery bypass graft surgery, but 1 patient underwent percutaneous transluminal coronary angioplasty.

Follow-up: Follow-up data were obtained at week-to-month intervals via office visit, telephone or letter. The follow-up period began on the day of AMI and ended on the date of last contact, initiation of antiarrhythmic treatment, or death. For arrhythmia-free survival analysis, the follow-up period for patients with spontaneous, sustained VT ended on the date of the first occurrence of arrhythmia. Spontaneous occurrence of arrhythmia was defined as a documented occurrence of either sustained VT or ventricular fibrillation. Sudden/arrhythmic death was defined as death within 1 hour from onset of symptoms or death resulting as a consequence of electrocardiographically registered ventricular arrhythmias.

Statistical analysis: Continuous values were expressed as mean ± 1 standard deviation. Comparisons of continuous variables were made by using Student's *t* test after validation of a normal distribution by the

TABLE II Clinical and Angiographic Characteristics of Patients Grouped by Response to Programmed Ventricular Stimulation on Day 19

	SMVT (n = 12)	SPVT, NSMVT, NSPVT (n = 10)	No Inducible Arrhythmia (n = 10)
Age (yrs)	62 ± 10	56 ± 11	64 ± 7
M/F	10/2	9/1	5/5
VT–CL (ms)	216 ± 32	194 ± 17	—
No. of ES required	2.9 ± 0.4 (2–3)	2.6 ± 0.8 (1–3)	—
Location of infarction			
Anterior	9 (75%)	8 (80%)	5 (50%)
Others	3 (25%)	2 (20%)	5 (50%)
Peak CK (IU/liter)	1,935 ± 1,538	1,200 ± 746	1,436 ± 1,284
PTCA	2 (17%)	2 (20%)	1 (10%)
No. of diseased vessels	2.2 ± 0.8	1.9 ± 1.1	1.9 ± 0.9
LV aneurysm	5 (42%)	1 (10%)	2 (20%)
Ejection fraction (%)	33 ± 15	36 ± 17	57 ± 18
		p = 0.02	
		p = 0.003	
Cardiac index (liters/min/m²)	2.2 ± 0.4	2.9 ± 0.5	3.1 ± 0.6
		p = 0.002	
		p < 0.001	
LV end-diastolic pressure (mm Hg)	24 ± 7	20 ± 6	21 ± 5
Holter Lown grade			
IVb	3 (25%)	0 (0%)	2 (20%)
IVa	1 (8%)	2 (20%)	2 (20%)
I–III	6 (50%)	7 (70%)	3 (30%)
0	2 (17%)	1 (10%)	3 (30%)

CL = cycle length; ES = extrastimuli; NSMVT = nonsustained monomorphic ventricular tachycardia; NSPVT = nonsustained polymorphic ventricular tachycardia; SMVT = sustained monomorphic ventricular tachycardia; SPVT = sustained polymorphic ventricular tachycardia; other abbreviations as in Table I.

Wilk-Shapiro test.[15] Dichotomous variables were analyzed by using Fisher's exact probability test. Survival curves were calculated by using the Kaplan-Meier method,[16] and the Mantel-Cox statistic[17] was used for comparing survivor functions across groups. Actuarial probabilities of survival and freedom from arrhythmias were expressed as a value ± 1 standard error. A p value <0.05 was accepted as statistically significant.

RESULTS

Induced ventricular arrhythmias (Figure 1): On day 19, sustained monomorphic VT was induced in 12 patients (38%), sustained polymorphic VT in 8 (25%), nonsustained monomorphic VT in 1 (3%), nonsustained polymorphic VT in 1 (3%), and no inducible arrhythmia in 10 (31%). On day 36, sustained monomorphic VT, nonsustained monomorphic VT and nonsustained polymorphic VT were induced in 8 patients each (25%), and no inducible arrhythmia in 8 (25%). Of 12 patients who had inducible sustained monomorphic VT on day 19, 7 had noninducibility of sustained monomorphic VT on day 36. Of 20 patients who had noninducibility of sustained monomorphic VT on day 19, 3 had inducible sustained monomorphic VT on day 36.

Relation between inducible ventricular arrhythmias and clinical characteristics: Relations between the inducibility of arrhythmias on days 19 (Table II) and 36 (Table III) and clinical characteristics were analyzed separately. On day 19, patients who had inducible sustained monomorphic VT had a significantly lower ejection fraction than patients with no inducible arrhythmia ($p = 0.003$), and had a lower cardiac index than patients with other inducible arrhythmias ($p = 0.002$) and

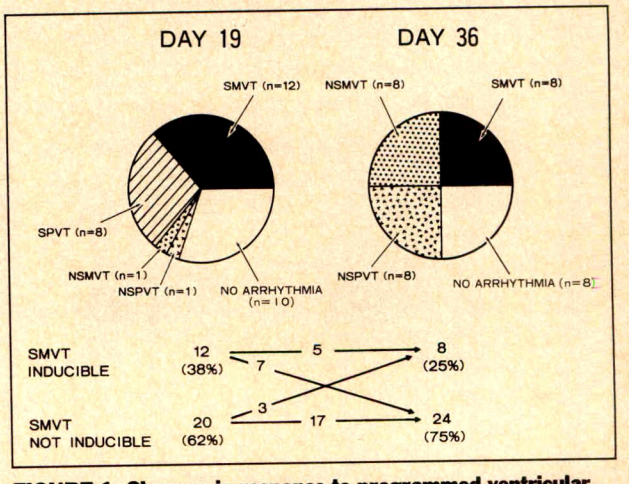


FIGURE 1. Changes in response to programmed ventricular stimulation. NSMVT = nonsustained monomorphic ventricular tachycardia; NSPVT = nonsustained polymorphic ventricular tachycardia; SMVT = sustained monomorphic ventricular tachycardia; SPVT = sustained polymorphic ventricular tachycardia.

TABLE III Clinical and Angiographic Characteristics of Patients Grouped by Response to Programmed Ventricular Stimulation on Day 36

	SMVT (n = 8)	SPVT, NSMVT, NSPVT (n = 16)	No Inducible Arrhythmia (n = 8)
Age (yrs)	65 ± 9	58 ± 11	63 ± 6
M/F	7/1	13/3	4/4
VT–CL (ms)	234 ± 44	215 ± 26	—
No. of ES required	2.4 ± 0.7 (2–3)	2.8 ± 0.4 (2–3)	—
Location of infarction			
Anterior	6 (75%)	9 (56%)	7 (88%)
Others	2 (25%)	7 (44%)	1 (12%)
Peak CK (IU/liter)	1,258 ± 700	1,512 ± 1,722	1,892 ± 1,049
PTCA	0 (0%)	4 (25%)	1 (13%)
No. of diseased vessels	2.3 ± 1.0	2.1 ± 1.1	1.6 ± 0.7
LV aneurysm	4 (50%)	3 (19%)	1 (13%)
Ejection fraction (%)	29 ± 8	47 ± 21	49 ± 20
		p = 0.007	
			p = 0.03
Cardiac index (liters/min/m²)	2.4 ± 0.6	2.8 ± 0.6	3.0 ± 0.6
LV end-diastolic pressure (mm Hg)	21 ± 5	25 ± 7	19 ± 4
Holter Lown grade			
IVb	3 (38%)	0 (0%)	0 (0%)
IVa	2 (24%)	1 (16%)	2 (25%)
I–III	3 (38%)	9 (56%)	5 (63%)
0	0 (0%)	6 (38%)	1 (12%)
IVb/0–IVa	3/5	0/16	0/8
	p = 0.03		
IVa–IVb/0–III	5/3	1/15	2/6
	p = 0.007		

Abbreviations as in Tables I and II.

patients with no inducible arrhythmia ($p < 0.001$). On day 36, patients who had inducible sustained monomorphic VT had a significantly lower ejection fraction than patients with other inducible arrhythmias ($p = 0.007$) and patients with no inducible arrhythmia ($p = 0.03$), and had a higher incidence of Holter Lown's grade IV than patients with other inducible arrhythmias ($p = 0.007$). There was no significant difference in other variables.

Holter monitoring (Figure 2): On day 19, 5 patients (16%) had Holter monitor grade IVb, 5 (16%) had grade IVa, 16 (50%) had grade I to III, and 6 (18%) had no ventricular arrhythmias (grade 0). On day 36, 3 patients (9%) had grade IVb, 5 (16%) had grade IVa, 17 (53%) had grade I to III, and 7 (22%) had no ventricular arrhythmias. Of 5 patients who had Holter grade IVb on day 19, 3 had grade 0 to IVa on day 36. Of 21 patients who did not have Holter grade IVb on day 19, 1 had grade IVb on day 36.

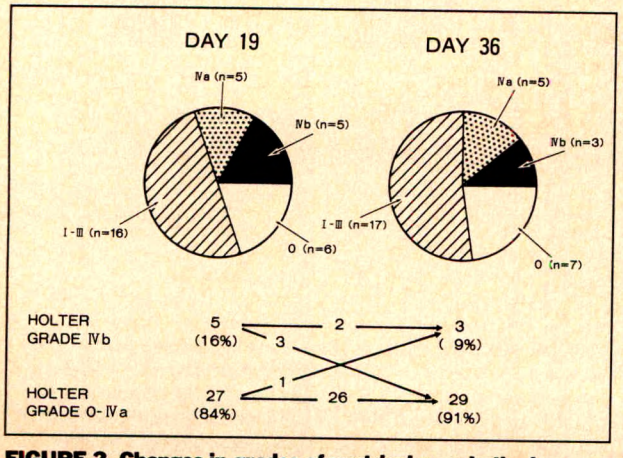


FIGURE 2. Changes in grades of ventricular arrhythmia.

Clinical follow-up: During the mean follow-up period of 21 ± 8 months (up to 33 months), 2 patients died suddenly and 3 had spontaneous occurrence of sustained VT. Another patient died of a noncardiac cause. All sudden deaths and spontaneous occurrences of sustained VT occurred within the first year after AMI. The 1-year probability of remaining free of arrhythmic events for the entire study population was 84 ± 6%, and the probability of survival from sudden/arrhythmic death at 1 year was 94 ± 4%.

Inducibility in relation to arrhythmic events: There were arrhythmic events (sudden cardiac death or spontaneous occurrence of sustained VT) in 4 of 12 patients (33%) who had inducible sustained monomorphic VT on day 19, compared with 1 of 20 patients (5%) with no inducible sustained monomorphic VT on day 19. The 1-year probability of remaining free of arrhythmic events was 67 ± 14% for patients with inducible VT on

day 19 and 95 ± 5% for patients with no inducible VT on day 19. Inducible sustained monomorphic VT on day 19 had a significantly poorer prognosis than no inducible sustained monomorphic VT ($p = 0.037$) (Figure 3). There were arrhythmic events in 5 of 8 patients (63%) who had inducible sustained monomorphic VT on day 36, compared with none of 24 patients with no inducible sustained monomorphic VT on day 36. The 1-year probability of remaining free of arrhythmic events was 38 ± 17% for patients with inducible VT on day 36 and 100% for patients with no inducible VT on day 36. Inducible sustained monomorphic VT on day 36 had a significantly poorer prognosis than no inducible sustained monomorphic VT ($p < 0.001$) (Figure 4).

Holter monitor grade in relation to arrhythmic events: There were arrhythmic events in 3 of 5 patients (60%) with Holter grade IVb on day 19, compared with 2 of 27 patients (7%) with grade 0 to IVa on day 19. The 1-year probability of remaining free of arrhythmic events was 40 ± 22% for patients with grade IVb on day 19 and 93 ± 5% for patients with grade 0 to IVa on day 19. Holter grade IVb on day 19 had a significantly poorer prognosis than grade 0 to IVa on day 19 ($p = 0.019$) (Figure 5). There were arrhythmic events in 2 of 3 patients (67%) with grade IVb on day 36, compared with 3 of 29 patients (10%) with grade 0 to IVa on day 36. The 1-year probability of remaining free of arrhythmic events was 33 ± 27% for patients

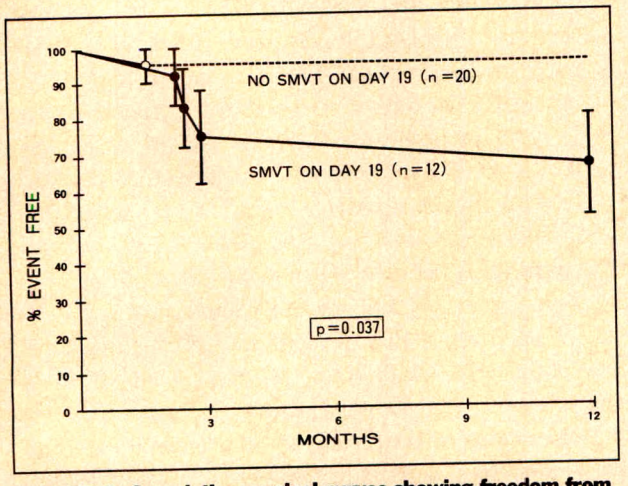


FIGURE 3. Cumulative survival curves showing freedom from arrhythmic events in postinfarction patients with inducible sustained monomorphic ventricular tachycardia (SMVT) and no inducible SMVT on day 19. Inducible SMVT on day 19 had a significantly poorer prognosis than no inducible SMVT ($p = 0.037$). *Vertical bars* represent 1 standard error.

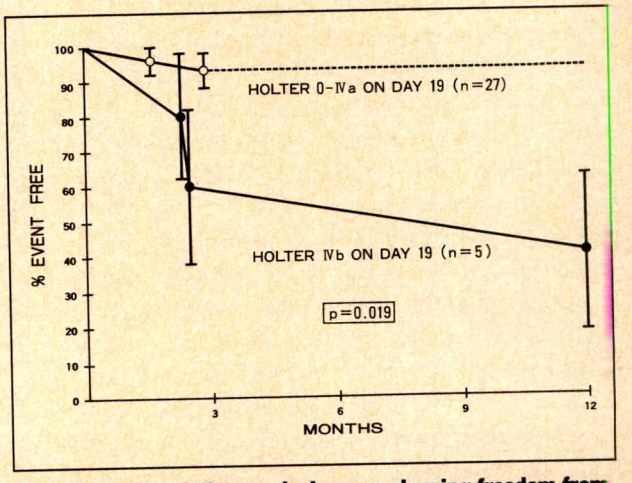


FIGURE 5. Cumulative survival curves showing freedom from arrhythmic events in postinfarction patients with detected Holter Lown's grade 0 to IVa and grade IVb on day 19. Holter Lown's grade IVb on day 19 had a significantly poorer prognosis than grade 0 to IVa on day 19 ($p = 0.019$). Format as in Figure 3.

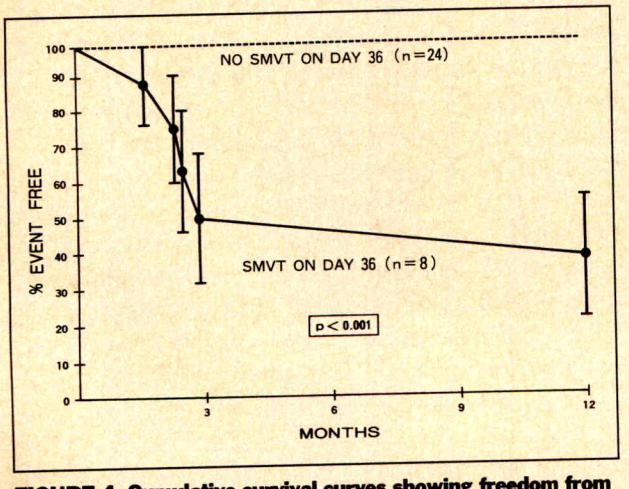


FIGURE 4. Cumulative survival curves showing freedom from arrhythmic events in postinfarction patients with inducible sustained monomorphic ventricular tachycardia (SMVT) and no inducible SMVT on day 36. Inducible SMVT on day 36 had a significantly poorer prognosis than no inducible SMVT ($p < 0.001$). Format as in Figure 3.

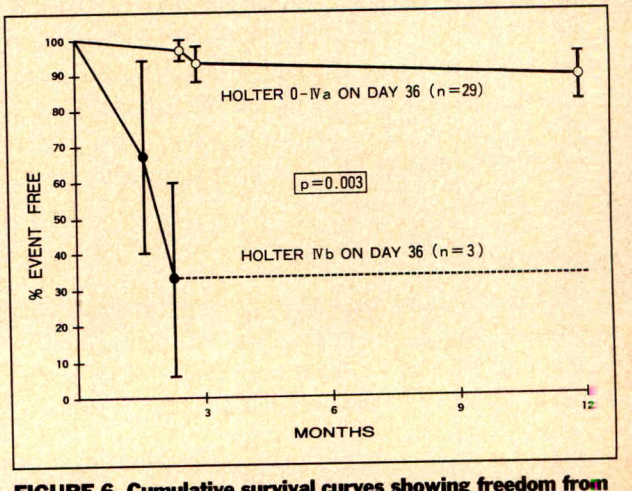


FIGURE 6. Cumulative survival curves showing freedom from arrhythmic events in postinfarction patients with detected Holter Lown's grade 0 to IVa and grade IVb on day 36. Holter Lown's grade IVb on day 36 had a significantly poorer prognosis than grade 0 to IVa on day 36 ($p = 0.003$). Format as in Figure 3.

TABLE IV Comparison of Prognostic Factors

Prognostic Factor	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Predictive Accuracy (%)
EF <40%	80	70	33	95	72
Holter grade IVb					
Day 19	60	93	60	93	88
Day 36	40	96	66	90	88
Inducible SMVT					
Day 19	80	70	33	95	72
Day 36	100	89	63	100	91

EF = ejection fraction; other abbreviations as in Table II.

with grade IVb on day 36 and 90 ± 6% for patients with grade 0 to IVa on day 36. Holter grade IVb on day 36 had a significantly poorer prognosis than grade 0 to IVa on day 36 ($p = 0.003$) (Figure 6).

Analysis of prognostic factors: Univariate analysis (comparison of Kaplan-Meier curves[16]) revealed the following variables to be predictive of arrhythmic events: ejection fraction <40% ($p = 0.040$), inducible sustained monomorphic VT on day 19 ($p = 0.037$), inducible sustained monomorphic VT on day 36 ($p < 0.001$), Holter grade IVb on day 19 ($p = 0.019$), and Holter grade IVb on day 36 ($p = 0.003$). None of the remaining variables were related to arrhythmic events. Multivariate analysis with use of the Cox proportional hazard model[17] could not be performed in this study because of the relatively small sample size.

Comparison of prognostic factors: Comparisons of significant prognostic factors are summarized in Table IV. In the prediction of future arrhythmic events, the inducibility of sustained monomorphic VT on day 36 had a sensitivity of 100%, a specificity of 89%, a positive predictive value of 63% and a negative predictive value of 100%, whereas values for Holter monitor grade IVb on day 36 were 40, 96, 66 and 90%, respectively. Among the prognostic factors, the inducibility of sustained monomorphic VT on day 36 had the highest sensitivity and negative predictive value, and Holter grade IVb on day 36 had the highest specificity and positive predictive value.

DISCUSSION

This study shows that the timing of programmed ventricular stimulation after AMI influences the inducibility of VT and its ability to predict sudden cardiac death and the occurrence of sustained ventricular tachyarrhythmias.

Previous studies of programmed ventricular stimulation in postinfarction patients: Since the report of Green et al,[1] the usefulness of programmed ventricular stimulation to identify patients at high risk of sudden cardiac death or sustained VT occurrence after AMI has been evaluated in ≥11 series involving over 1,000 patients.[1-11] These studies vary greatly in their conclusions. This disparity may be due to differences in methodology, such as the stimulation protocol, definition of induced arrhythmias, intervals from the onset of AMI to study, or length of the follow-up period. Our study suggests that the timing of the stimulation study after AMI is an important consideration that might explain some of the differences among previous studies.

In the 8 previous studies[1-8] that have suggested that ventricular stimulation might be useful, the mean intervals from the onset of AMI to study ranged from 11 to 54 days (mean 24). On the other hand, in the 3 studies[9-11] concluding that programmed stimulation was less useful, the mean intervals from AMI to study ranged from 11 to 22 days (mean 13).

Importance of the timing of programmed ventricular stimulation: Several experimental[18-20] and clinical studies[21-23] investigated the influence of timing of ventricular stimulation on the inducibility of VT. In our canine experiment,[20] the inducibility of VT was labile before day 15 of AMI and it reached a constant phase after day 15, when serial stimulation studies were performed on days 8, 15, 22 and 29 after AMI. Kuck et al[22] studied 18 patients with AMI on days 5 and 24 with a stimulation protocol using a maximum of 3 right ventricular extrastimuli. In their study, sustained VT was inducible in 2 patients on day 5 and in 6 on day 24 after AMI. They showed that the timing of ventricular stimulation after AMI influenced the inducibility of sustained VT, but they could not prove that timing of study influenced its predictive ability, because no patient died suddenly or developed spontaneous sustained arrhythmias during a follow-up period of 24 months. The favorable clinical course may be due in part to differences in left ventricular ejection fraction. The mean ejection fraction of their patients was 47 ± 9%, and only 3 (17%) had an ejection fraction <40%, whereas the mean ejection fraction of our patients was 41 ± 19%, and 12 (38%) had an ejection fraction <40%. Roy et al[23] reported the results of programmed

ventricular stimulation in 21 patients with AMI who had had inducible VT (≥6 beats) on 12 ± 2 days after MI. Of 21 patients, 8 had inducible sustained monomorphic VT on day 12. Patients were restudied 8 ± 2 months after AMI, and 4 of 8 still had inducible sustained monomorphic VT. No patient had sustained monomorphic VT initiated at the late study if it had not been initiated at the time of the early study. However, their study population consisted of patients with inducible VT on day 12, and their stimulation protocol was less aggressive, using up to 2 extrastimuli delivered from the right ventricular apex. During the follow-up period of 17 months, only 1 patient with inducible sustained monomorphic VT at both studies died suddenly.

In the present study, univariate analysis revealed that inducibilities of sustained monomorphic VT both at the early (day 19) and late studies (day 36) were predictive of sudden death and the occurrence of clinical sustained ventricular tachyarrhythmias. However, inducibility of sustained monomorphic VT at the late study had a higher sensitivity, specificity, and positive and negative predictive values than at the early study. This suggests that the timing of programmed ventricular stimulation study after AMI also influences the prognostic value of induced VT.

Other prognostic factors: The other prognostic factors were left ventricular ejection fraction <40% and Holter grade IVb on days 19 and 36. The best noninvasive prediction of arrhythmic events was obtained from Holter grade IVb on day 36. However, Holter grade IVb on day 36 was less sensitive (40%) than either inducible sustained monomorphic VT on days 19 or 36 in predicting subsequent arrhythmic events.

Time-dependent predictors of inducible sustained monomorphic ventricular tachycardia: The variables predictive of inducible sustained monomorphic VT in patients with AMI have been reported. Iesaka et al[8] demonstrated that the presence of a left ventricular aneurysm and Holter grade IVb were independent predictors of inducible sustained monomorphic VT. However, when the inducibility of VT varies over time, the predictors of inducibility should also be considered to be time-dependent variables. In the present study, the variables associated with inducible sustained monomorphic VT on day 19 were lower ejection fraction and cardiac index, and the variables associated with inducible sustained monomorphic VT on day 36 were lower ejection fraction and Holter grade IVb. These predictors may be useful in screening patients with proper indications for electrophysiologic study.

Clinical implications: On day 19, 8 patients (25%) had inducible sustained polymorphic VT (including ventricular fibrillation), which was of little prognostic value in our series and required direct-current cardioversion. On day 36, no patient had inducible sustained polymorphic VT. This suggests that the longer time interval reduces nonspecific and nondiagnostic responses, such as polymorphic VT. Programmed ventricular stimulation ≥4 weeks after AMI increased its predictive value.

Study limitations: Nine patients were treated with β blockers during the follow-up period and 1 patient underwent percutaneous transluminal coronary angioplasty. These might have influenced clinical outcome.

During the follow-up period, 2 patients died suddenly. It is very difficult to identify patients who have sudden arrhythmic death from a primary electrical event rather than from acute ischemia.

No patient died between the early and the late studies. However, a potentially high-risk period is known to exist within the first few weeks after AMI. Waiting for electrophysiologic stability might present high risk to certain patients. Therefore, all of the factors influencing the optimal timing of stimulation may not yet be fully appreciated.

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Relation of Left Ventricular Volume and Function Over One Year After Acute Myocardial Infarction to Infarct Size Determined by Technetium-99m Sestamibi

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Twenty patients with a first acute myocardial infarction (AMI) (15 anterior, 5 inferior) who received successful reperfusion therapy underwent tomographic imaging with technetium-99m (Tc-99m) sestamibi and radionuclide ventriculography at discharge, 6 weeks, and 1 year after AMI. Patency of the infarct-related artery after reperfusion (thrombolysis, 8 patients; coronary angioplasty, 12 patients) was confirmed by angiography in all patients. Tc-99m sestamibi perfusion defect at discharge (a measure of infarct size) was quantitated using previous methods and expressed as a percentage of the left ventricle (28 ± 19%, range 0 to 59%). This perfusion defect size correlated closely with ejection fraction at discharge ($r = -0.87$), 6 weeks ($r = -0.81$) and at 1 year ($r = -0.78$, all $p < 0.0001$). Perfusion defect size at discharge also correlated closely with end-systolic volume index at discharge ($r = 0.71$, $p < 0.0005$), 6 weeks ($r = 0.63$, $p < 0.005$) and at 1 year ($r = 0.76$, $p < 0.0001$). Perfusion defect size at discharge did not correlate significantly with end-diastolic volume index at discharge or at 6 weeks, but did correlate at 1 year ($r = 0.66$, $p < 0.005$). There was no significant group change in end-systolic or end-diastolic volume indexes from discharge to 1 year later, although 7 patients had definite individual changes in end-diastolic volume index (3 increased and 4 decreased). There was no relation between defect size and late changes in end-systolic volume index, but there was a weak correlation between defect size and late changes in end-diastolic volume index ($r = 0.42$, $p = 0.07$). Tc-99m sestamibi perfusion defect at discharge correlates with ejection fraction, and end-diastolic and end-systolic volume indexes 1 year after AMI. In most patients with patent infarct-related arteries after AMI, there does not appear to be a significant overall increase in ventricular volume during the first year after infarction.

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Left ventricular (LV) ejection fraction and LV end-systolic volume have independently been shown to have important prognostic value in patients after acute myocardial infarction (AMI).[1,2] Technetium-99m (Tc-99m) sestamibi tomographic estimation of infarct size has been shown to correlate with ejection fraction at hospital discharge and 6 weeks later in patients after AMI.[3,4] However, the correlation of Tc-99m sestamibi infarct size with subsequent changes in ventricular volumes after AMI has not been described.

Ventricular dilatation can occur early after AMI in proportion to infarct size[5] and may continue for many months thereafter,[6] presumably secondary to slippage and stretching of myocyte bundles and myofibrils.[7] Attenuation of this response has been demonstrated in animal models with late reperfusion therapy and open vessels independent of time or actual degree of myocardial salvage.[8] Limited studies in patients with patent infarct-related vessels have demonstrated less ventricular dilatation after AMI compared with studies of patients with persistent vessel occlusion.[9] Thus, the patency of the infarct-related artery may influence the degree of LV dilatation after AMI, perhaps independent of final infarct size.

This study examined the relation between tomographic Tc-99m sestamibi estimation of infarct size and early and late ventricular volume measurements in patients with patent infarct-related arteries.

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TABLE I Characteristics of the 20 Patients

Pt.	Age (yr) & Sex	IRA	MI Location	Reperfusion Modality	Reperfusion Time (min)	Infarct Size (%LV)	Ejection Fraction			ESVI (ml/m²)			EDVI (ml/m²)		
							Dis.	6 Wk.	1 Yr.	Dis.	6 Wk.	1 Yr.	Dis.	6 Wk.	1 Yr.
1	57M	LAD	Anterior	rt-PA	88	17	0.43	0.47	0.44	75	97	87	130	180	151
2	57M	Right	Inferior	rt-PA	120	22	0.44	0.39	0.49	81	108	52	141	174	101
3	64M	LAD	Anterior	rt-PA	215	58	0.23	0.40	0.39	99	96	113	126	157	180
4	50M	LAD	Anterior	PTCA	109	17	0.45	0.40	0.42	51	82	62	91	134	104
5	42M	LAD	Anterior	PTCA	168	38	0.33	0.34	0.45	85	88	78	126	131	139
6	70M	LAD	Anterior	PTCA	781	59	0.33	0.36	0.46	87	79	61	128	120	111
7	60M	LAD	Anterior	PTCA	348	44	0.33	0.43	0.32	91	86	121	134	149	174
8	71M	LAD	Anterior	PTCA	540	31	0.43	0.38	0.41	34	53	52	60	84	86
9	43M	LAD	Anterior	rt-PA	245	17	0.45	0.46	0.48	95	70	65	169	126	122
10	60M	LAD	Anterior	rt-PA	133	42	0.29	0.41	0.37	129	105	119	180	176	185
11	43M	Right	Inferior	PTCA	96	23	0.35	0.52	0.42	65	43	71	98	88	121
12	62M	LAD	Anterior	PTCA	772	16	0.64	0.56	0.62	41	67	53	114	148	136
13	46M	Right	Inferior	PTCA	291	11	0.57	0.54	0.61	32	29	35	74	61	88
14	58M	LC	Inferior	PTCA	206	0	0.69	0.71	0.66	28	18	16	89	60	45
15	40M	LAD	Anterior	PTCA	163	48	0.32	0.28	0.37	79	113	99	114	153	155
16	78F	LAD	Anterior	rt-PA	95	0	0.69	0.67	0.78	23	36	11	73	105	50
17	55M	LAD	Anterior	PTCA	323	46	0.29	0.45	0.35	77	69	77	106	122	117
18	78F	Right	Inferior	rt-PA	241	0	0.62	0.64	0.57	42	31	37	108	84	85
19	78F	LAD	Anterior	rt-PA	395	51	0.32	0.37	0.36	76	60	77	110	94	119
20	50M	LAD	Anterior	PTCA	330	13	0.76	0.64	0.66	16	37	41	64	102	120

Dis. = discharge; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; IRA = infarct-related artery; LAD = left anterior descending artery; LC = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue-type plasminogen activator.

METHODS

The study group consisted of a consecutive series of patients enrolled in a prospective trial of Tc-99m sestamibi from June 1987 to September 1989 who met the following criteria: (1) chest pain of ≥30 minutes duration, (2) electrocardiographic ST elevation of ≥0.1 mV in ≥2 leads in the same vascular territory, (3) successful reperfusion therapy within 18 hours of the onset of chest pain documented by coronary angiography, (4) elevated creatine kinase-MB isoenzymes within 24 hours of chest pain, (5) resting radionuclide angiography performed at discharge, 6 weeks and 1 year after AMI. No patient had recurrent AMI or congestive heart failure between hospital discharge and 1 year after radionuclide angiography.

Reperfusion therapy: Intravenous thrombolysis was performed with recombinant tissue-type plasminogen activator (8 patients) using previously described methods.[10] Primary coronary angioplasty was performed on 12 patients.

Coronary angiography: Patients receiving primary coronary angioplasty had arteriograms recorded immediately after balloon inflations, whereas patients who received thrombolysis generally had angiograms recorded later in their hospital course (mean time to angiography, 2 ± 2 days). The infarct-related artery was identified by analysis of the acute electrocardiographic ST-segment changes, the site of regional wall motion abnormalities on contrast left ventriculography, and the coronary angiogram. All patients had a patent (grade II or III) infarct-related artery after reperfusion therapy.[10]

Radionuclide studies: Tomographic radionuclide acquisitions were performed at discharge 1 to 6 hours after injection of 20 to 30 mCi of Tc-99m sestamibi using previously described techniques.[3] Quantitation of the extent of LV hypoperfusion was performed using a short-axis 5-slice method. Circumferential count profiles were generated for representative apical, midventricular, basal, and 2 intermediate slices. Quantitation of the perfusion defect as a percentage of the left ventricle was performed using this 5-slice modification of our previously described 3-slice method,[3] which has previously correlated closely with perfusion defect size in phantoms,[11] pathologic infarct size in animal models,[12,13] and ejection fraction and creatine kinase enzyme levels in clinical studies.[3,4,14]

Radionuclide ventriculography with Tc-99m–labeled red blood cells was performed at hospital discharge (1 day after Tc-99m sestamibi imaging), at 6 weeks and 1 year later. Radionuclide images were acquired and processed using previously described techniques.[15] Ejection fraction was calculated from the background corrected LV counts versus time curve. Ventricular volumes were determined using a count-based method corrected for body surface area and a previously reported regression equation.[16] On the basis of a previous study, definite changes in end-systolic and end-diastolic volume indexes for individual patients were considered to be 26 and 38 ml/m², respectively.[17]

Statistical evaluation: Simple linear regression was used to correlate Tc-99m sestamibi perfusion defect size with ejection fraction and ventricular volumes. Repeated-measures analysis of variance was used to compare changes over time for ventricular volumes, ejection fraction and hemodynamic parameters. A Kruskal-Wallis test was used to compare Tc-99m sestamibi perfusion defect size between patients with and without a definite change in ventricular volume.

RESULTS

The study group consisted of 20 patients (17 men and 3 women, mean age ± standard deviation 58 ± 12 years [range 40 to 78] [Table I]). Reperfusion therapy was successful in all patients (time, 4.3 ± 3.3 hours; range, 1.5 to 13 hours; 10 patients were treated after 4 hours). There were 12 patients who received primary coronary angioplasty (time, 5.7 ± 3.9 hours) and 8 patients who received thrombolytic therapy (time, 3.2 ± 1.7 hours, difference not significant when compared with angioplasty). The left anterior descending artery was the infarct-related vessel in all 15 patients with anterior infarction. Four of 5 patients with inferior infarction had the right coronary artery as the infarct-related vessel; the remaining patient had occlusion of the left circumflex artery. Three patients had coronary angioplasty between discharge and 1 year; all had restenosis of the infarct-related artery (70 to 95% stenosis) but none had total arterial occlusion. The mean time from AMI to discharge was 8 ± 2 days. Most patients (90%) were taking antianginal medications at the time of discharge radionuclide angiography; 70% received nitrate preparations, 50% received β-adrenergic receptor blockers, and 40% received calcium antagonists. One patient was taking an angiotensin-converting enzyme inhibitor. At 1 year, 70% of patients were still receiving antianginal medications.

Radionuclide measurements: Infarct size estimated by Tc-99m sestamibi tomographic imaging was 28 ± 19% of the left ventricle (range 0 to 59%). There was no significant change in ejection fraction between discharge (0.45 ± 0.16), 6 weeks (0.47 ± 0.12), and 1 year (0.48 ± 0.13) (Table I). There was no significant group change in end-systolic or end-diastolic volume in-

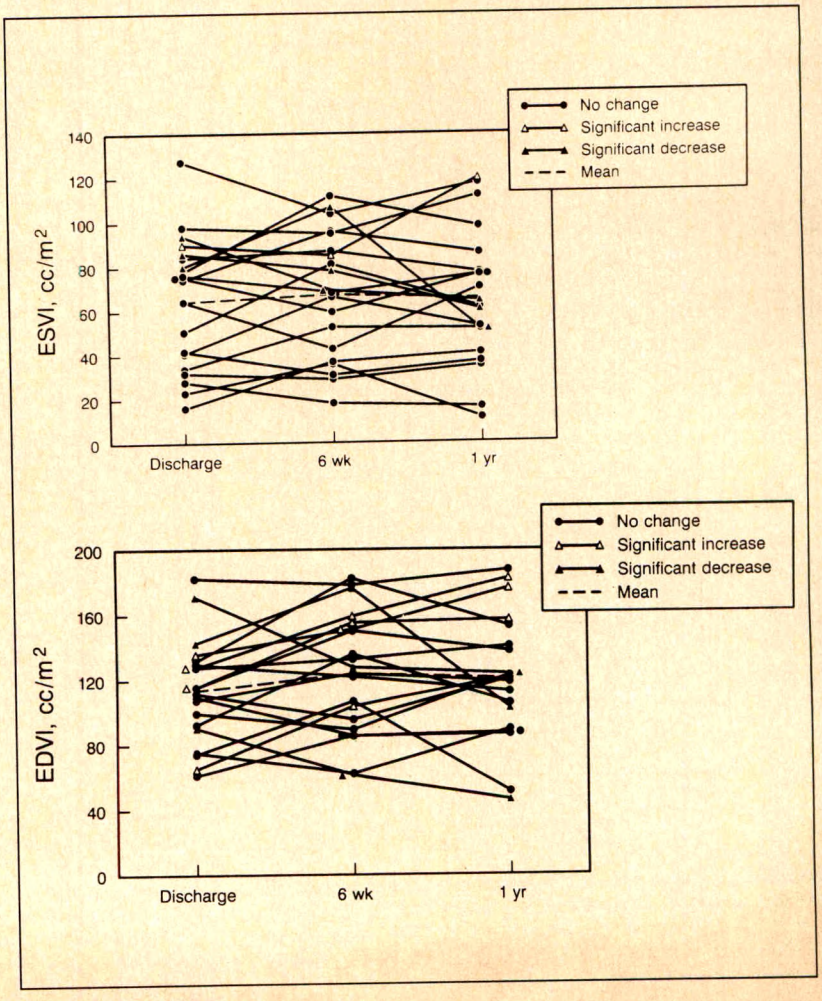


FIGURE 1. ***Top,*** **end-systolic volume index (ESVI) and** ***(bottom)*** **end-diastolic volume index (EDVI) measured at discharge, 6 weeks and 1 year after acute myocardial infarction. A significant change between measurements was considered to be 26 and 38 ml/m², respectively.**

dexes between discharge, 6 weeks or 1 year (Figure 1). Only 3 patients had a definite individual decrease in end-systolic volume index at 1 year; 1 patient had a definite individual increase. Seven patients (3 with increased and 4 with decreased end-diastolic volume indexes) had a definite individual change in end-diastolic volume index compared with measurements at discharge (Figure 1). There was no significant difference in diastolic blood pressure during the 3 time points of radionuclide acquisition. However, there was a significant increase in systolic blood pressure at 1 year (125 ± 15 mm Hg) compared with 6 weeks (115 ± 15 mm Hg ± <0.05), but not when compared with discharge (118 ± 11 mm Hg). There was a significant decline in heart rate from discharge (66 ± 12 beats/min) to 6 weeks (57 ± 10 beats/min, p <0.005), which persisted at 1 year (58 ± 10 beats/min).

Correlation between technetium-99m sestamibi infarct size and radionuclide ventriculography (Figure 2): There was a close correlation between infarct size estimated by Tc-99m sestamibi tomographic imaging and ejection fraction at discharge ($r = -0.87$, $p < 0.0001$), 6 weeks ($r = -0.81$, $p < 0.0001$) and 1 year ($r = -0.78$, $p < 0.0001$). There was a similar close correlation between Tc-99m sestamibi infarct size and end-systolic volume index at discharge ($r = 0.71$, $p < 0.0005$), 6 weeks ($r = 0.63$, $p < 0.005$) and 1 year ($r = 0.76$, $p < 0.0001$). End-diastolic volume index did

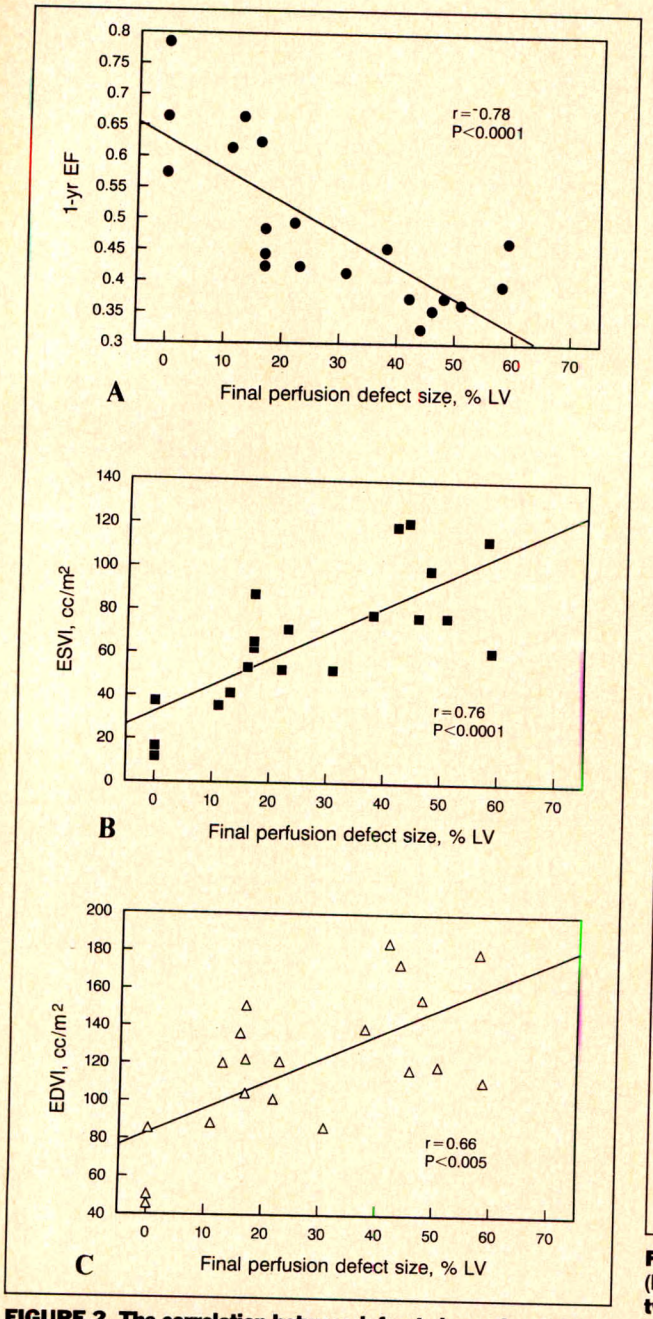


FIGURE 2. The correlation between infarct size estimated by technetium-99m sestamibi at discharge and *(A)* ejection fraction (EF), *(B)* end-systolic volume index (ESVI), and *(C)* end-diastolic volume index (EDVI) measured at 1 year after infarction. LV = left ventricle.

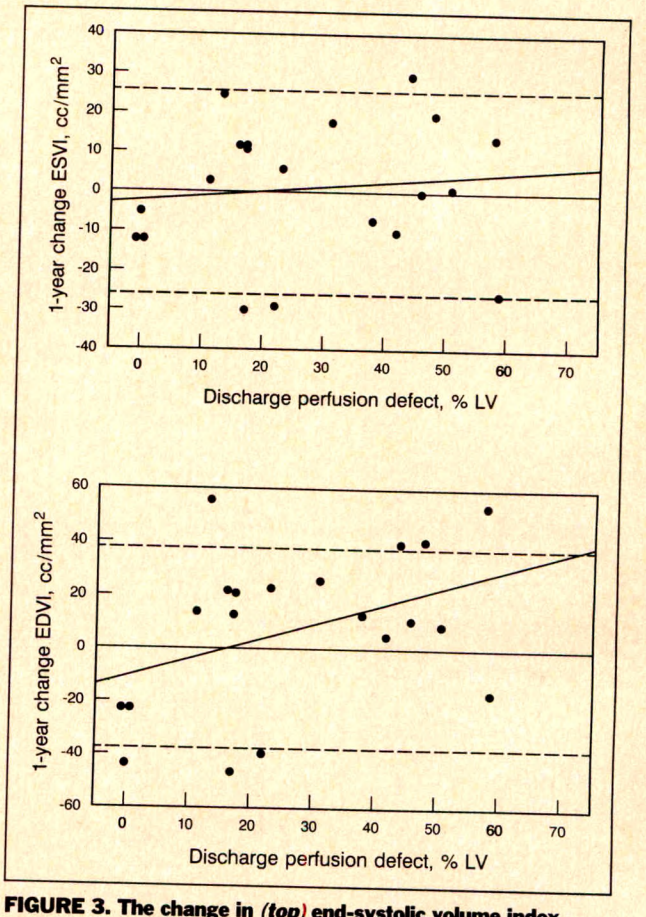


FIGURE 3. The change in *(top)* end-systolic volume index (ESVI) and *(bottom)* end-diastolic volume index (EDVI) between hospital discharge and 1 year (1 year volume-discharge volume) compared with infarct size estimated by technetium-99m sestamibi as percentage of the left ventricle. There was no significant correlation between the change in these volumes and infarct size. *Dotted lines* represent the change in volume considered to be significant (26 and 38 ml/m², respectively).

not correlate significantly with the infarct size at discharge or at 6 weeks ($r = 0.39$ and $r = 0.40$) but did at 1 year ($r = 0.66$, $p < 0.005$). Tc-99m sestamibi perfusion defect size at discharge did not correlate with the change in end-systolic volume index between discharge and 1 year (Figure 3). Perfusion defect size correlated weakly with the late change in end-diastolic volume index ($r = 0.42$, $p = 0.07$).

DISCUSSION

Tc-99m sestamibi is valuable for assessing myocardium at risk and final infarct size using tomographic imaging, and correlates closely with ejection fraction at discharge and after discharge.[3,4] The present study reaffirms these relations and further demonstrates that infarct size quantitated at discharge continues to correlate closely with ejection fraction at 1 year after infarction.

End-systolic LV volume has been shown to have powerful prognostic value and has been proposed as the major determinant of survival after AMI.[2] The present study demonstrates a close association between Tc-99m sestamibi infarct size and end-systolic volume index at discharge, at 6 weeks and at 1 year after AMI. Although the prognostic value of Tc-99m sestamibi infarct size is unknown, these data show that it is closely associated with 2 major prognostic indicators after infarction. In contrast to previous clinical studies, infarct size did not correlate strongly with the extent of change in ventricular volumes.[18] We believe this may be due to patency of the infarct-related artery in this patient group. Persistent occlusion of an infarct-related artery has been associated with ventricular dilatation.[19] Attenuation of ventricular dilatation after AMI has been shown in both animal and clinical studies when patency of the infarct-related artery is established.[8,9]

The present study showed no significant change in ventricular volumes between discharge and 1 year in patients with successful reperfusion therapy, 50% of whom were treated after 4 hours. Many patients were given nitrate preparations, which may be associated with an attenuation of ventricular dilatation.[20] One patient was receiving an angiotensin-converting enzyme inhibitor. Because few patients demonstrated a significant increase in LV volumes, it is not surprising that tomographic Tc-99m sestamibi infarct size did not correlate strongly with late changes in ventricular volumes.

These findings are in contrast to a previous study from this laboratory where patients successfully treated with thrombolytic therapy still demonstrated slight but significant LV dilatation between 1 and 6 weeks, although less than those with occluded arteries.[9] The results of our previous study were heavily influenced by 2 patients who demonstrated marked LV dilatation; the remaining patients with successful reperfusion therapy in that study showed little change.

Study limitations: The study group is small and the power to detect subtle differences is therefore low. In addition, there is a preponderance of patients with anterior infarction in the study group, so little can be concluded regarding patients with inferior infarction. However, it has been shown that patients with anterior infarction are more likely to demonstrate ventricular dilatation after AMI.[5] Quantitation of perfusion defect size using a threshold method measures the extent of a perfusion abnormality but does not consider the severity of the defect. Perfusion defect severity may have important implications for residual flow.

A potential source of error is that ventricular volumes may change early in the course of AMI. It would be of benefit to assess ventricular volumes earlier than hospital discharge but such determinations were not available in this study group. Error inherent in radionuclide ventriculography volume determinations is high[17] and, therefore, small changes in volume will be difficult to detect using this technique. Future studies using more accurate noninvasive techniques to assess cardiac volume changes after myocardial infarction may be necessary to detect such small changes.

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Percutaneous Transluminal Angioplasty of Aortocoronary Venous Bypass Grafts and Effect of the Caliber of the Grafted Coronary Artery on Graft Stenosis

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The influence of morphologic parameters on the recurrence of stenosis after percutaneous transluminal coronary angioplasty of 49 stenoses in aortocoronary venous bypass grafts of 41 patients was investigated. Vessel dimensions were measured quantitatively. Angioplasty was successful in 46 stenoses (94%) of 38 patients (93%). In 35 patients (92% of successfully treated patients) with 42 stenoses, control angiography was performed after a mean interval of 189 ± 186 days. In 9 patients (26%), 9 stenoses (21%) had recurred. The diameter of the grafted coronary artery distal to the anastomosis was significantly smaller in grafted arteries with than without recurrent stenoses (1.92 ± 0.52 vs 2.45 ± 0.50 mm; p <0.01). Recurrence also correlated with the ratio between graft diameter and coronary artery diameter >1.35 (p <0.02) and with the stenosis length >10 mm before angioplasty (p <0.01). Graft age, graft diameter and stenosis location in the graft had no significant influence on recurrence.

Thus, the diameter of the grafted coronary artery and the length of the critical stenosis are parameters for recurrence after angioplasty of graft stenoses and should be considered in the selection of patients for this intervention.

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Percutaneous transluminal angioplasty of stenoses in aortocoronary venous bypass grafts represents a promising alternative to repeat operation. However, recurrence of stenosis after successful angioplasty is a major limitation of the method's long-term success.[1–11] Based on animal experiments suggesting an influence of coronary blood flow on intimal tissue proliferation, we investigated whether recurrence of stenosis after graft angioplasty may depend on an indirect parameter of blood flow—the caliber of the grafted coronary artery.[12–14]

METHODS

Patients: Forty-one consecutive patients (35 men and 6 women, mean age ± standard deviation 57 ± 6 years [range 46 to 72]) underwent angioplasty for angina pectoris or positive exercise-stress test, or both, at an average interval of 40 ± 39 months (mean 1 to 132) after coronary bypass graft surgery. An exercise stress test was performed in all patients before angioplasty; results were positive (ST-segment depression >0.1 mm) in 23 patients, negative in 3 and could not be definitely judged in 15. In 18 of 30 patients with previous myocardial infarction, the stenosed graft supplied the infarct region (angiographically documented akinetic area), which was always small.

In all, patients with 44 stenoses and 5 occlusions in 42 grafts underwent angioplasty. The grafts supplied the left anterior descending artery in 26 patients, left circumflex artery branches in 6 and the right coronary artery in 10. In 8 patients 2 stenoses were treated, i.e., in 7 patients stenoses in identical grafts were treated and in 1 patient stenoses in different grafts were treated. Seven of 49 narrowings (14%) were located at the proximal graft anastomosis, 30 in the graft body (61%) and 12 at the distal anastomosis (25%).

Procedure of angioplasty: During angioplasty 15,000 U of heparin as well as several bolus doses of 0.1 mg nitroglycerin were injected into the treated graft. Nitrates were also regularly administered at control coronary angiography. Angioplasty was performed with 8Fr bypass-guiding catheters (Schneider) and monorail-type balloon catheters (Schneider-Piccolino or

TABLE I Angina Pectoris Before Angioplasty (all patients) and at 3 to 24 Weeks After Angioplasty (38 patients with successful treatment)

Angina Pectoris (CCS)	Before Angioplasty (n = 41)	After Angioplasty (n = 38)
I	1 (2%)	17 (45%)
II	8 (20%)	9 (24%)
III	19 (46%)	8 (21%)
IV	13 (32%)	4 (10%)
	3.1 ± 0.8*	2.0 ± 1.0

*Mean ± standard deviation.
CCS = Canadian Cardiovascular Society classification.

TABLE II Angiographic Recurrence Rate After Successful Angioplasty of 42 Graft Stenoses (35 patients): Correlation with Anatomic Parameters and Graft Age

	Recurrence (n = 9)	No Recurrence (n = 26)	
Diameter of grafted coronary artery (mm)	1.92 ± 0.52	2.45 ± 0.50	p <0.01
Diameter of grafted coronary artery <2.2 mm	7/9 St. (78%)	9/33 St. (27%)	p <0.01
Diameter of graft (mm)	3.07 ± 0.43	3.06 ± 0.46	NS
Graft–coronary artery diameter ratio	1.75 ± 0.70	1.33 ± 0.45	NS
Graft–coronary artery diameter ratio >1.35	7/9 St. (78%)	10/33 St. (30%)	p <0.02
Graft age (months)	33 ± 30	43 ± 41	NS
Graft to infarct region	3/9 (33%)	13/27 (48%)	NS

Values are expressed as mean ± standard deviation: unpaired *t* test; frequencies: chi-square test.
NS = not significant; St. = stenoses.

ACS-RX), with sizes from 2.5 to 3.5 mm. In stenoses of the graft body and of the proximal anastomosis, the size of the balloon was selected according to the graft caliber, and in stenoses of the distal anastomosis the size was chosen in accordance with the diameter of the native coronary artery. Recanalizations of bypass occlusions were performed with Schneider-Shiley guidewires (0.014 inch).

Quantitative analysis of cine films: Cine frames were analyzed from 2 orthogonal, always identical, angiographic projections before and after angioplasty, as well as in the control angiograms. The vessel contours were exactly traced from a Tagarno projector. Measurements were performed with a precision magnification lens (accuracy 0.05 mm). This method had been validated by repeated analyses of 20 graft stenoses and grafted coronary arteries by the same investigator within 2 weeks. In repeated measurements of all angiographic parameters, the standard deviations of the mean differences were 0.12 mm for minimal stenosis diameter, 0.11 mm for reference diameter, 4.2% for percent area stenosis, 1.1 mm for stenosis length and 0.10 mm for the diameter of the native coronary artery.

The following parameters were measured: graft diameter, minimal stenosis diameter, reference diameter (average diameter of angiographically normal adjacent proximal and distal subsegments), stenosis length and percent area stenosis. The latter was calculated by comparison of the luminal cross-sectional area in the stenosis and at the reference site as interpolated from measurements in the 2 orthogonal views on the supposition of an elliptic stenosis lumen. The diameter of the grafted coronary artery was analyzed a few millimeters distal to the graft anastomosis. The site of measurement was determined by an experienced cardiologist who was unaware of the patients' follow-up angiograms. A "balloon-graft ratio" was calculated from the minimal balloon diameter during its last inflation in the stenosis and the reference diameter of the bypass graft (see before).[6,15] Calibration of the cine frames was performed with reference to the guiding and coronary catheters.

Statistics: Stenoses with and without recurrence were compared with 2-sided statistical tests. For quantitative variables the modified *t* test with separate variance estimation was performed; for categorical variables the chi-square test was used. For paired comparisons the paired *t* test was applied. A stepwise logistic regression was performed on all parameters under scrutiny to estimate the combination of variables that best predicts whether or not the stenoses will be recurrent.

RESULTS

Before angioplasty, the interpolated percent area stenosis of the 49 lesions was 87 ± 9% on average (72 to 100%). Angioplasty was successful (reduction of the percent area stenosis by >20 to <70%) in 46 of 49 narrowings (94%) (including 3 of 5 graft occlusions), in 39 of 42 grafts (93%) and in 38 of 41 patients (93%). In these stenoses, percent area stenosis immediately after angioplasty was 39 ± 16% (0 to 69%). Two of the 3 patients with nonsuccessful angioplasty were treated medically and 1 underwent repeat operation. No procedure-related clinical events occurred during or after angioplasty.

Of the 38 patients with successful angioplasty, 35 (92%) with 42 stenoses in 36 grafts underwent control coronary angiography after an interval of 189 ± 186 days (mean 25 to 799). Stenosis recurrence defined as percent area stenosis ≥70% was found at 9 sites (21%) in 9 grafts (25%) of 9 patients (26%). In 3 patients with recurrence of 1 stenosis, a second stenosis, which had been simultaneously dilated in the same graft, revealed permanent success. Six patients with recurrence underwent repeat angioplasty, 1 underwent repeat operation and 2 were treated medically. Severity of angina pectoris at 3 to 24 weeks after angioplasty is listed in Table I; angina pectoris was not significantly different between patients with and without recurrence (1.8 ± 0.8 vs 2.0 ± 1.0 Canadian Cardiovascular Society classification).

TABLE III Correlation of Recurrence with Stenosis Morphology and Localization

	Recurrence (n = 9)	No Recurrence (n = 26)	
Cross section after angioplasty (mm^2)	4.7 ± 1.1	4.6 ± 1.7	NS
% Area stenosis after angioplasty (%)	39 ± 6	39 ± 19	NS
St. with % area St. after angioplasty >30%	8/9 St. (89%)	21/33 St. (64%)	NS
St. length before angioplasty (mm)	11.7 ± 8.5	7.1 ± 6.0	NS
St. with length before angioplasty >10 mm	5/8 St. (62%)	4/32 St. (12%)	p <0.01
St. in proximal graft anastomosis	1/5 St. (20%)	4/5 St. (80%)	
St. in graft body	7/25 St. (28%)	18/25 St. (72%)	NS
St. in distal graft anastomosis	1/12 St. (8%)	11/12 St. (92%)	

Statistics and abbreviations as in Table II.

The incidence of recurrence was set in relation to some morphologic and technical parameters (Tables II to IV). A univariate analysis found that the average coronary diameter distal to grafts with and without stenosis recurrence was significantly different: 1.92 ± 0.52 vs 2.45 ± 0.50 mm ($p < 0.01$). When the 25 graft body stenoses were analyzed separately, recurrence was found in 7 (28%) (see later). The average diameter of the grafted coronary artery in this subgroup was 1.59 ± 0.46 mm in recurrent stenoses vs 2.44 ± 0.54 mm in grafted arteries without recurrent stenoses ($p < 0.01$). The diameter of the bypass graft did not significantly influence stenosis recurrence. However, the ratio between graft diameter and coronary artery diameter was found to be >1.35 in 78% of stenoses with and in 30% of stenoses without recurrence ($p < 0.02$) (Table II). Stenosis length of >10 mm before angioplasty was measured in 62% of recurrent stenoses (1 occlusion before angioplasty) and in 12% of grafted arteries without recurrence of stenoses (also 1 occlusion before angioplasty) ($p < 0.01$). Stenoses with a percent area stenosis >30% immediately after angioplasty tended to occur more often (difference not significant). In stenoses of the distal graft anastomosis recurrence was somewhat less frequent than in stenoses of other localizations (Table III). Stenoses in which the balloon was inflated >2 times recurred somewhat more frequently (difference not significant). Maximal inflation pressure and balloon-graft ratio had no influence on recurrence (Table IV).

Stepwise logistic regression was performed on all parameters analyzed to estimate the combination of parameters that best predicted recurrence of stenosis. Two variables entered the model, the diameter of the grafted coronary artery and the length of stenosis. The goodness-of-fit chi-square to test that the model fits the data adequately had a p value of 0.81.

TABLE IV Correlation of Procedural Factors with Stenosis Recurrence

	Recurrence (n = 9)	No Recurrence (n = 26)	
No. of balloon inflations	4.4 ± 2.6	3.6 ± 2.0	NS
St. with >2 balloon inflations	9/9 St. (100%)	25/33 St. (76%)	NS
Maximal inflation pressure (atm)	11.8 ± 3.1	10.4 ± 2.7	NS
Balloon–graft ratio	0.91 ± 0.14	0.91 ± 0.11	NS

Statistics and abbreviations as in Table II.

DISCUSSION

In the present study, the success rate of angioplasty amounted to 94%. This corresponds to the results of other studies on angioplasty of bypass grafts, which, however, used various definitions of success.[2,3,7,9,11] We defined a reduction of percent area stenosis to <70% as successful; stenosis recurrence was defined as an increase of percent area stenosis to ≥70%. This "threshold" was chosen because only coronary stenoses with a reduction of the arterial lumen by ≥70% have been demonstrated to be hemodynamically significant.[16]

In the present study, a nearly complete angiographic follow-up after angioplasty was obtained. In previous studies, the angiographic follow-up rates varied between 30 and 60% of patients.[1,3,5–7,9,10,15,17] In these studies, stenoses of the distal graft anastomosis recurred less frequently than did stenoses in other localizations.[1,4,5] Our findings confirmed these data, although the correlation was not significant; one possible reason might be that stenoses of the distal graft anastomosis are frequently caused by suture-induced compression associated with platelet adhesion.[18] These stenoses can be dilated without major tissue traumatization, which provokes subendothelial proliferation.

We could demonstrate a significant correlation between the diameter of the grafted coronary artery and recurrence of graft stenosis. Stenosis recurrence correlated best with the diameter of the native coronary artery <2.2 mm. The diameter of a coronary artery may be regarded as a correlate of the myocardial mass dependent on the vessel's blood supply and of its blood flow.[13,14] Previous infarctions in the myocardial region supplied by the grafted coronary artery, which could be associated with a reduced blood flow, had no influence on the appearance of restenosis.

In animal experiments, coronary flow rates and shear stress were demonstrated to correlate negatively with spontaneous subendothelial proliferation in venous

bypass grafts, which can cause recurrence of stenosis after angioplasty.[12,19] Because the lumina of venous bypass grafts usually are broader than those of native coronary arteries, the intimal shear stress at identical flow rates is considerably lower in the bypass grafts. Thus, intimal shear stress in grafts must decrease with an increasing graft–coronary artery diameter ratio, which corresponds to our finding of an increased recurrence rate of stenoses in grafts with a high graft–coronary artery diameter ratio.

A positive correlation between stenosis length and recurrence after angioplasty of a native coronary artery has been reported.[20] In the present study, such a correlation was also demonstrated for graft stenoses. The reason may be that in larger stenoses a greater intimal area is exposed to injury and platelet adhesion, which enhances the probability of stenosis recurrence.[21] After angioplasty of native coronary arteries, a positive correlation between stenosis recurrence and percent stenosis immediately after angioplasty has been reported, which may be due to unfavorable flow characteristics of high-grade stenoses.[6,11,22] Also, in our study on graft angioplasty, stenoses of >30% after angioplasty recurred more often than those <30%, although this was not statistically significant. In contrast to previous studies we found no significant influence of the age of the bypass grafts and of the balloon-graft ratio on recurrence of graft stenosis.[6,9,15]

In conclusion, stenosis localization in the graft and the degree of stenosis immediately after angioplasty may have an influence on recurrence of stenosis after angioplasty of aortocoronary bypass grafts. Stenosis recurrence correlated negatively with the diameter of the grafted coronary artery distal to the anastomosis. In addition, stenosis length was shown to be associated with an increased risk of recurrence. These parameters should be considered in the selection of graft stenoses for angioplasty.

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Effects of a Multidimensional Cardiopulmonary Rehabilitation Program on Psychosocial Function

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The effects of participation in a structured, outpatient cardiac rehabilitation program on psychosocial function after acute myocardial infarction or coronary artery bypass surgery, or both, were evaluated prospectively in 141 patients who were married or living with "a significant other" (89% men, mean [± standard deviation] age 63 ± 9 years old). Forty-one patients who were participants in a 3-month cardiac rehabilitation program were compared with 100 patients who did not participate in a formal program. On average, patients in both groups were well educated, older Caucasians who had minimal cardiac dysfunction (New York Heart Association class I or II). Patients in the 2 groups were not different at baseline in sociodemographic or clinical characteristics or in any of the dependent measures of anxiety, depression, psychosocial adjustment to illness or marital adjustment. Six months after initial testing, patients who attended cardiac rehabilitation were significantly less anxious ($F[1,139] = 5.09$, $p = 0.03$), less depressed ($F[1,139] = 8.39$, $p = 0.004$), had better psychosocial adjustment ($F[1,139] = 5.87$, $p = 0.02$), and were more satisfied with their marriages ($F[1,139] = 8.6$, $p = 0.004$) than nonparticipants. The findings support the effectiveness of group cardiac rehabilitation for this subgroup of patients in facilitating their psychosocial recovery after an acute cardiac event.

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Patient participation in an exercise-based cardiac rehabilitation program may minimize the physical and emotional disability associated with myocardial infarction and coronary artery bypass surgery, but controversy exists over the exact nature of the benefits of such programs and their value in relation to their cost.[1–5] Recent reviews and meta-analyses of experimental data have documented the following benefits: reduced mortality, improved functional capacity, improved symptom-limited maximal oxygen uptake and reduced cardiac risk factors.[4–6] However, many studies have not supported the commonly held belief that participation in a cardiac rehabilitation program improves psychological well-being.[7–10] In general, the programs subjected to systematic assessment have focused on exercise training and excluded education and counseling components.[7,11] This study compares the psychosocial adaptation of patients who participated in a multidimensional cardiac rehabilitation program with that of patients who did not.

METHODS

Patients: Patients were recruited during the 4 years between May 1985 and April 1989 from 6 large metropolitan area hospitals in Los Angeles County as part of an ongoing study to test the effects of teaching cardiopulmonary resuscitation to family members of cardiac patients. Patients received no intervention as part of the cardiopulmonary resuscitation study. Patients were included if they had the following: (1) a myocardial infarction or coronary artery bypass surgery within the past 12 months, (2) were literate in English, (3) aged 25 to 80 years, and (4) living with a spouse or significant other. Patients were excluded if they had a significant chronic illness other than heart disease or a history of psychiatric illness. The sociodemographic and clinical characteristics of the patient sample are summarized in Table I. On average, patients were older Caucasian men (mean ± standard deviation age 63 ± 9 years old, range 33 to 80), well educated, with minimal cardiac symptoms and with supportive spouses.

Cardiac rehabilitation: Forty-one patients participated in a structured outpatient cardiac rehabilitation program. The remaining 100 patients, who served as a comparison group, were largely patients discharged

TABLE I Comparison of Group Characteristics

	Cardiac Rehabilitation	No Cardiac Rehabilitation	p Value
No. of subjects	41	100	
Gender			NS
Male (%)	38 (93)	88 (88)	
Female (%)	3 (7)	12 (12)	
Marital status			NS
Married (%)	39 (95)	97 (97)	
Single (%)	2 (5)	3 (3)	
Work status			NS
Employed (%)	16 (39)	46 (46)	
Unemployed (%)	2 (5)	4 (4)	
Sick leave (%)	3 (7)	5 (5)	
Retired (%)	20 (49)	45 (45)	
Income			NS
0–$9,999 (%)	0 (0)	1 (1)	
$10,000–39,999 (%)	9 (22)	26 (26)	
> $40,000 (%)	26 (63)	60 (60)	
No answer (%)	6 (15)	8 (8)	
Cardiac diagnosis*			NS
Myocardial infarction (%)	28 (68)	70 (70)	
Cardiac bypass surgery (%)	24 (56)	66 (66)	
Angina (%)	30 (73)	71 (71)	
Age (yrs)	63 ± 8	63 ± 10	NS
Time from cardiac event (mos)	4 ± 3	5 ± 3	NS
Years of education	14 ± 3	15 ± 3	NS
NYHA functional class	1 ± 0.3	1 ± 0.3	NS

Mean values are ± standard deviation.
*Categories not mutually exclusive.
NS = difference not statistically significant; NYHA = New York Heart Association.

TABLE II Comparison of Psychosocial Function Between Cardiac Rehabilitation (n = 41) and Noncardiac Rehabilitation (n = 100) Groups

	Cardiac Rehabilitation		No Cardiac Rehabilitation	
	Baseline	6 Months	Baseline	6 Months
Anxiety	7 ± 4	5 ± 4	7 ± 5	7 ± 4
Depression	12 ± 7	8 ± 7	13 ± 7	13 ± 7
Psychosocial adjustment	42 ± 9	36 ± 8	44 ± 11	42 ± 11
Marital adjustment	115 ± 20	121 ± 16	114 ± 17	111 ± 18

Anxiety: higher scores indicate increased anxiety; depression: higher scores indicate increased depression; psychosocial adjustment: higher scores indicate poorer adjustment; marital adjustment: higher scores indicate better adjustment.

from hospitals that did not have cardiac rehabilitation programs. Four cardiac rehabilitation programs were represented. Although they were in different locations, they shared a number of similarities; all were nurse-supervised, with patients attending 3 monitored exercise sessions per week for 12 weeks. All programs included a detailed health evaluation of the patient, initial patient-spouse interview and mutual goal-setting, stress management classes, risk factor counseling and education. The philosophy of the programs emphasized patient responsibility and accountability.

Instruments: Psychosocial functioning was assessed by measuring levels of anxiety, depression, marital adjustment and overall psychosocial adjustment to illness. Data were collected at baseline and at 6 months through 3 mailed questionnaires. The Multiple Affect Adjective Checklist was used to measure the state of anxiety and depression.[12,13] It consists of 132 alphabetically arranged adjectives with instructions to check words that describe feelings over the previous week. Scores for anxiety range from 0 to 21. For anxiety, scores of ≤7 are within normal range. Scores for depression range from 0 to 40, with 11 considered moderate clinical depression.

The Psychosocial Adjustment to Illness Scale is designed to measure the changes a person has experienced in a variety of psychological and social dimensions as a result of a physical illness.[14–17] Organized into a 46-item self-report questionnaire, the scale reflects 7 dimensions: health care orientation, vocational environment, domestic environment, sexual relations, extended family relations, social environment and psychological distress. Marital adjustment was measured by the Spanier Dyadic Adjustment Scale.[18] The 32-item questionnaire was designed for use with either married or unmarried cohabiting couples. The scale measures marital adjustment along the 4 dimensions of marital satisfaction, dyadic cohesion, consensus and affection. All questionnaires have established reliability and validity and have been used in a variety of clinical populations, including patients with cardiac disease.

Data analysis: Baseline group characteristics were compared to identify any differences between the 2 study groups by using independent *t* tests and chi-square. Comparison of baseline values of the dependent variables between the groups was accomplished by analysis of variance. The hypothesis that the 2 groups differed for the dependent variables of anxiety, depression, total psychosocial adjustment and marital satisfaction was examined by using multivariate analysis of variance with post hoc comparison by univariate analysis of variance to identify sources of difference. Statistical significance was set at a p value of 0.05. Continuous data are presented as mean ± standard deviation.

RESULTS

There were no significant differences between the cardiac rehabilitation group and the group not attending cardiac rehabilitation in sociodemographic and clinical characteristics (Table I) or in baseline psychosocial states (Table II). However, there were significant differences between the 2 groups over time for the dependent variables ($F[4,136] = 4.32$, $p = 0.02$) using Pillais' criterion. Results of the evaluation of assumptions of normality and homogeneity of variance-covariance ma-

trixes were satisfactory. Post hoc comparisons by univariate analysis of variance revealed that patients who participated in a cardiac rehabilitation program were significantly less anxious ($F[1,139] = 5.09$, $p = 0.03$), less depressed ($F[1,139] = 8.39$, $p = 0.004$), had better psychosocial adjustment ($F[1,139] = 5.87$, $p = 0.02$), and were more satisfied with their marriages ($F[1,139] = 8.6$, $p = 0.004$) at 6 months follow-up than patients who did not participate in formal cardiac rehabilitation (Table II).

Although patients did not receive any intervention as part of the cardiopulmonary resuscitation training study from which the subjects for this study were recruited, we used participation in the cardiopulmonary resuscitation intervention group as a factor in the analysis to eliminate the possibility that family assignment offers a competing explanation of patient group differences. There was no significant difference between the groups, whether or not family members had learned cardiopulmonary resuscitation ($F[12,423] = 0.56$, $p = 0.87$).

DISCUSSION

Although these findings are limited by the nonrandomized design, participation in an outpatient, monitored cardiac rehabilitation program resulted in improved psychosocial function at 6-month follow-up. Patients who participated in the cardiac rehabilitation program were significantly less anxious and less depressed, had better psychosocial adjustment and greater marital satisfaction than patients who did not participate. A possible explanation for these positive findings is that the programs tested in this trial used a multidimensional approach to recovery. Previous investigators have suggested that specific psychologically oriented interventions are required to reap positive psychological benefits. For example, in a study of 106 postmyocardial infarction patients randomized to either a group counseling program or an exercise training program, exercise training significantly reduced fatigue, increased exercise work capacity and promoted feelings of independence.[19] Patients in the group receiving a counseling intervention were significantly less anxious and depressed at 6 months than patients in the group receiving an exercise training intervention. The mechanism usually proposed for the positive psychological effect of exercise training is that increased levels of fitness lead to enhanced self-esteem; however, in several studies the changes in emotional functioning that were associated with participation in an aerobic training class were independent of actual changes in fitness.[20,21] Thus, exercise alone may not be powerful enough to alter the psychological and social recovery of patients after a cardiac event, whereas a program that operates on several levels simultaneously (i.e., physical, emotional, social) evokes such changes.

In most cardiac rehabilitation studies, patients enter a rehabilitation program with relatively normal scores of psychosocial measures, allowing little room for improvement.[7,10] Those investigators who enrolled patients with moderate to severe psychosocial disturbances did show differences between experimental and control groups.[19] Although most patients in the present study also scored within normal ranges at baseline, significant improvement in psychosocial status was documented in the rehabilitation group, whereas the control group remained relatively unchanged. This result supports the effectiveness of the multidimensional approach to rehabilitation tested in the current study.

All patients in the current study were married or living with a significant other. There is some evidence that family support of participation in cardiac rehabilitation is an important predictor of psychosocial recovery.[11] Because all previous studies of the psychosocial effects of cardiac rehabilitation have used a sample of both married and single patients, the positive results in the current study may also reflect a synergistic effect between participation in a rehabilitation program and spouse support.

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Efficacy and Safety of Intravenous Sotalol for Termination of Paroxysmal Supraventricular Tachycardia

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A double-blind, placebo-controlled, crossover, multicenter study was conducted to study the efficacy and safety of a single intravenous dose of sotalol (1.5 mg/kg over 10 minutes) in achieving normal sinus rhythm in paroxysmal supraventricular tachycardia (SVT) lasting ≥15 minutes. Patients were randomized to either sotalol or placebo as initial treatment, and if the SVT was not terminated a crossover was performed after 20 minutes.

A total of 43 patients were enrolled, 38 of whom with spontaneous (n = 14) or induced (n = 24) SVT were analyzed for sotalol efficacy. Most patients (n = 27) had atrioventricular (AV) nodal reentrant tachycardia, and an important subgroup (n = 11) had circus movement tachycardia, using an accessory pathway for retrograde conduction. The number of patients converting to sinus rhythm as a result of the initial treatment was significantly higher in the sotalol group than in the placebo group, for spontaneous ($p < 0.005$) as well as for induced tachycardia ($p < 0.001$). Sinus rhythm was achieved within 30 minutes in 83% of all patients who received sotalol as the first drug, compared with 16% of the patients first receiving placebo ($p < 0.0001$).

For sotalol safety analysis, 42 patients were included. A total of 37 patients received sotalol, 19 as the first treatment, and 18 as the second treatment, while 25 patients received placebo. A total of 15 possible adverse effects were reported, occurring in 10 patients with sotalol versus 4 with placebo. The only severe side effect (hypotension) necessitating termination of drug administration occurred with placebo. No proarrhythmic effects were observed. The intravenous administration of sotalol appears to be safe and effective for acute termination of supraventricular reentrant tachycardia.

(Am J Cardiol 1991;68:35–40)

Termination of paroxysmal supraventricular tachycardia (SVT) is usually achieved with vagal maneuvers or intravenous drugs, e.g., some calcium antagonists or adenosine.[1,2] The most widely used agent for this purpose is verapamil.[3] However, verapamil depresses myocardial contractility and can induce hypotension. If it is given to a patient receiving oral β blockers, sinus arrest can occur.[4] Verapamil can be life-threatening when it is given to patients with the Wolff-Parkinson-White syndrome and atrial fibrillation or to patients with ventricular tachycardia.[5–7] Several clinical studies were undertaken with other antiarrhythmic agents, such as adenosine and adenosine triphosphate. Despite its efficacy, mainly in children, its use is limited by adverse effects and early recurrence of arrhythmia.[2,8]

Sotalol, a β-blocking agent with additional class III antiarrhythmic properties, has been reported to cause significant increases in atrioventricular (AV) nodal and ventriculoatrial conduction times.[9,10] It is effective in preventing attacks of paroxysmal SVT in patients with the Wolff-Parkinson-White syndrome.[9,10] It is superior to metoprolol in the prevention of induction of SVT.[10] No controlled study has been performed for termination of paroxysmal SVT, and the ideal dosage is unknown. Reversion of SVT was achieved in only 5 of 12 patients who were given 0.4 mg/kg of sotalol.[11] Therefore, we assessed the efficacy and the safety of intravenous sotalol (1.5 mg/kg) in a double-blind, placebo-controlled, crossover study in patients with spontaneous and induced paroxysmal SVT.

METHODS

Patient selection: Paroxysmal SVT included AV nodal reentrant tachycardia and circus movement tachycardia with the use of overt or concealed bypass tracts. Patients with spontaneous paroxysmal SVT, de-

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TABLE I Patient Characteristics and Baseline Clinical Data

Study Group	Spontaneous SVT	Induced SVT
M/F	5/12	14/12
Age (yrs)	49 ± 15	37 ± 15
Weight (kg)	68 ± 11	73 ± 13
Type of SVT		
Atrial flutter	1	0
AVNT	16	14
CMT	0	12
Duration of tachycardia (hrs)	3.3	>0.25
Ventricular rate during SVT (beats/min)	172 ± 17	186 ± 28
Blood pressure during SVT		
Systolic (mm Hg)	118 ± 14	118 ± 17
Diastolic (mm Hg)	85 ± 17	83 ± 16

Values are mean ± standard deviation.
AVNT = atrioventricular nodal tachycardia; CMT = circus movement tachycardia; SVT = supraventricular tachycardia.

fined as tachycardia with a narrow QRS complex (<0.12 second) of ≥15 minutes' duration and a ventricular rate of >120 beats/min were eligible for the study. Patients with a sustained SVT with similar characteristics of ≥15 minutes' duration and induced by pacing were also included. Exclusion criteria were pregnancy, chronic obstructive pulmonary disease, second- or third-degree AV block, hypotension (systolic blood pressure <80 mm Hg) and heart failure. Other cardiovascular criteria for exclusion were a recent myocardial infarction (<1 month), recent coronary artery bypass graft surgery, active pericarditis or myocarditis, or both, digitalis toxicity, sick sinus syndrome, abnormally prolonged QTc interval (>0.45 second) and a diastolic blood pressure >115 mm Hg. Patients with previous treatment failure with sotalol (1.5 mg/kg intravenously and ≥320 mg/day orally) were also excluded. Previous therapy (within the last 6 hours) with verapamil, diltiazem, disopyramide, flecainide, β-adrenoceptor blockers and quinidine was a formal contraindication for entry, as was treatment with diuretics without potassium supplements or tri- or tetracyclic antidepressant therapy.

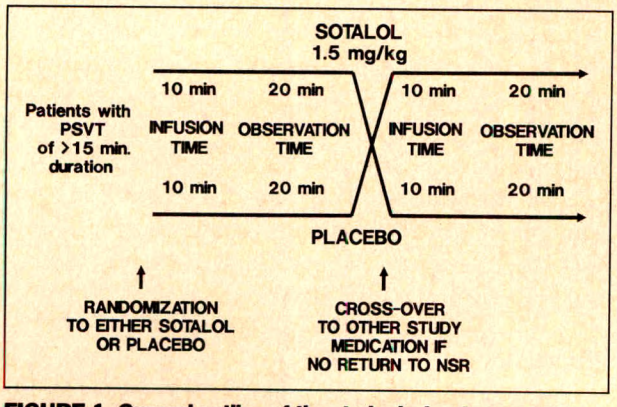


FIGURE 1. General outline of the study design for acute termination of paroxysmal supraventricular tachycardia (PSVT) with sotalol. NSR = normal sinus rhythm.

Study design: The study protocol and amendments were reviewed and approved by the Institutional Review Boards of all participating centers. Patients gave informed consent. The flow-chart of the study is shown in Figure 1. Test formulations were supplied by Bristol-Myers Pharmaceutical Research & Development Division. Each patient was assigned 2 identical boxes: 1 containing 4 placebo ampules and the other 4 active drug ampules. The order of administration was clearly indicated. Patients first received either sotalol (1.5 mg/kg) or saline over 10 minutes, followed by the other test medication if a return to sinus rhythm was not achieved within 30 minutes. This was the principal end point. The primary evaluations of safety were reports of on-therapy conditions, and measurements of vital signs. Special attention was given to the possibility of arrhythmia aggravation.

Statistical methods: Qualifying patients were randomized into 1 of the 2 treatment groups, depending on the first drug being administered. The primary efficacy sample excluded patients with major protocol violations. The safety sample included all patients treated. The differences between the treatment groups were assessed by using Fisher's exact test. Changes from baseline in electrocardiographic intervals and blood pressure were assessed by using Student's *t* test. Of 43 patients enrolled from 7 centers, 38 were evaluable. This sample size has a power of 65% to detect a significant difference at the 5% level, assuming a 10% response rate with placebo treatment and a 50% response rate with sotalol. Analyses of differences between centers have been performed.

Study population: A total of 43 patients (17 with spontaneous and 26 with induced tachycardia) were randomized. Table I lists the characteristics of the patients. There were no marked differences between the treatment groups in terms of cardiac history or functional status. Five patients were excluded from the primary efficacy analysis because of misdiagnosis (atrial flutter); return of sinus rhythm before a drug was given; misplacement of the infusion cannula, so that the drug was given subcutaneously and the infusion stopped after 8 minutes; hypotension; and wide QRS tachycardia. This left 38 patients suitable for assessment for sotalol efficacy. The patient in whom the SVT terminated before administration of the study drug was excluded from efficacy and safety analysis, so that 42 patients were assessed for sotalol safety.

Characteristics of baseline tachycardia: In this section only the patients included for sotalol efficacy analysis (n = 38) are described.

SPONTANEOUS TACHYCARDIA: The type of paroxysmal SVT was AV nodal tachycardia in 15 patients. No dif-

TABLE II Number of Patients Converting to Normal Sinus Rhythm During the Study Period, According to Type of Arrhythmia

	First Drug		Second Drug	
	Sotalol	Placebo	Sotalol	Placebo
Spontaneous AVNT	7/7 (100)	1/8 (13)	7/7 (100)	—
p Value	<0.005			
Induced AVNT	4/5 (80)	2/7 (29)	3/6 (50)	0/1 (0)
p Value	NS			
Induced CMT	4/6 (67)	0/5 (0)	4/5 (80)	0/1 (0)
p Value	0.045			

Numbers in parentheses are percentages. Fisher's exact test was performed only for the first study drug.
Abbreviations as in Table I.

ferences existed between placebo and sotalol groups. The mean duration of episodes and the ventricular rate were also similar.

INDUCED TACHYCARDIA: AV nodal tachycardia was diagnosed 12 times. The Wolff-Parkinson-White syndrome was observed in 4 patients. However, the induced arrhythmia in 1 of these was AV nodal tachycardia, and it is included in the former group. A concealed reciprocating tachycardia mechanism was present in 8 patients. This makes a total of 11 patients with circus movement tachycardia, with retrograde conduction over the accessory pathway and anterograde conduction over the AV node. The induced arrhythmia was sustained (>15 minutes) in all patients. No differences were observed between the sotalol and the placebo groups.

RESULTS

Efficacy: No concomitant antiarrhythmic medication was given. During the first 30-minute study period, all 7 spontaneous patients (100%) who received sotalol returned to sinus rhythm, compared with 1 of 8 (12.5%) in the placebo-treated patients. The difference was statistically significant ($p < 0.005$). In the patients with induced tachycardia, 8 of 11 patients (73%) treated with sotalol returned to sinus rhythm, compared with 2 of 12 patients (17%) treated with placebo ($p < 0.001$). Combining both types of patients gave an overall response rate of 83% with sotalol and 16% with placebo ($p < 0.0001$). All 7 patients with spontaneous tachycardia and persistent SVT after placebo treatment returned to sinus rhythm during the subsequent infusion period with sotalol. Seven of the 11 failures (64%) with induced SVT with placebo returned to sinus rhythm during the second infusion period with sotalol, compared with 0 of 2 failures (0%) with sotalol who received placebo as the second study drug.

Efficacy by type of supraventricular tachycardia: Results according to the type of SVT are summarized in Table II. For spontaneous tachycardia, the difference between sotalol and placebo was statistically significant: these patients all had AV nodal tachycardia. It remained significant when all patients with AV nodal tachycardia were combined. This difference was not evident for the group of patients with circus movement tachycardia (due to the small number of patients).

Time to conversion: Most patients ($n = 20$) returned to sinus rhythm within 10 minutes of the start of sotalol infusion. The mean (± standard deviation) time to conversion after the beginning of sotalol infusion for the group with spontaneous SVT was 9.38 ± 7.50 minutes, and for the induced SVT group it was 10.63 ± 8.85 minutes. The difference for the total number of patients is shown in Figure 2.

Changes in ventricular rate: Patients receiving sotalol as the first drug had an early decrease in ventricular rate before returning to sinus rhythm. There was no change in patients receiving placebo as the first drug. These differences were statistically significant after 2 minutes in the group with active treatment (decrease of 13 beats/min, compared with 1 beat/min for the placebo group). A similar trend was observed in the patients who failed to return to sinus rhythm, but the sample sizes were too small to detect a statistically significant difference.

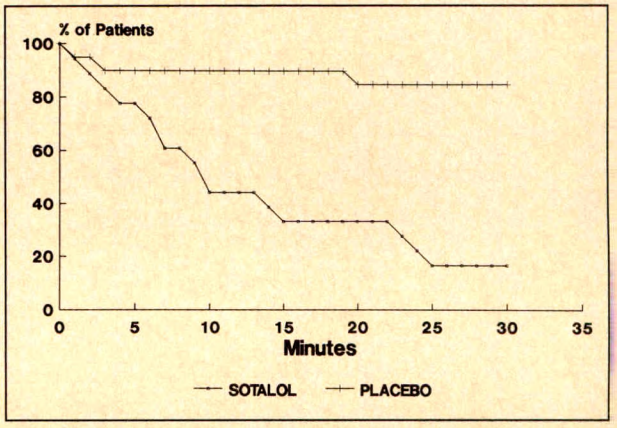


FIGURE 2. Time course of conversion to sinus rhythm and termination of paroxysmal supraventricular tachycardia in 20 patients treated with placebo and in 18 treated with sotalol (only data from the first study drug).

TABLE III Comparison of Adverse Effects and Arrhythmias During Treatment (n = 42)

	Placebo (n = 25)	Sotalol (n = 37)
Adverse Effects		
Hypotension	1	2
Presyncope/dizziness	1	1
Weakness	0	1
Chest pain	1	1
Vomiting	0	1
Others (minor)	0	2
Arrhythmias During Treatment		
Ventricular premature complexes	0	1
Nonsustained ventricular tachycardia	1	0
Polymorphic ventricular tachycardia	0	1
Atrial fibrillation	0	1

Mechanism of termination: The mechanism of termination could be determined in a reliable way in 21 responders (Figure 3). Three patients with AV nodal tachycardia receiving placebo had termination of tachycardia in an anterograde direction. In most patients suitable for analysis and conversion with sotalol (13 of 18), the SVT was terminated by slowing and blocking the retrograde pathway (the ventriculoatrial limb in 7 of 8 patients with circus movement tachycardia; the retrograde direction in 6 of 8 patients with AV nodal tachycardia). Sotalol terminated AV nodal tachycardia in the anterograde direction in 2 patients and circus movement tachycardia in a similar way in 1 patient. Other mechanisms of termination were observed in the remaining 2 patients with AV nodal tachycardia (Wenckebach block and supraventricular premature beats).

Hemodynamic effects: Transient increases in systolic and the diastolic blood pressures were observed in the few responders receiving placebo, whereas mild decreases in systolic and the diastolic blood pressures were observed in patients receiving sotalol. For the 3 patients who did not respond to sotalol, a small but significant initial decrease in systolic blood pressure was observed, compared with the placebo group.

Safety: A total of 37 patients were exposed to sotalol treatment. There were no deaths in this trial. Adverse effects are summarized in Table III. A total of 15 adverse effects were reported by 10 of the 37 patients (27%) who received sotalol, and by 4 of the 25 (16%)

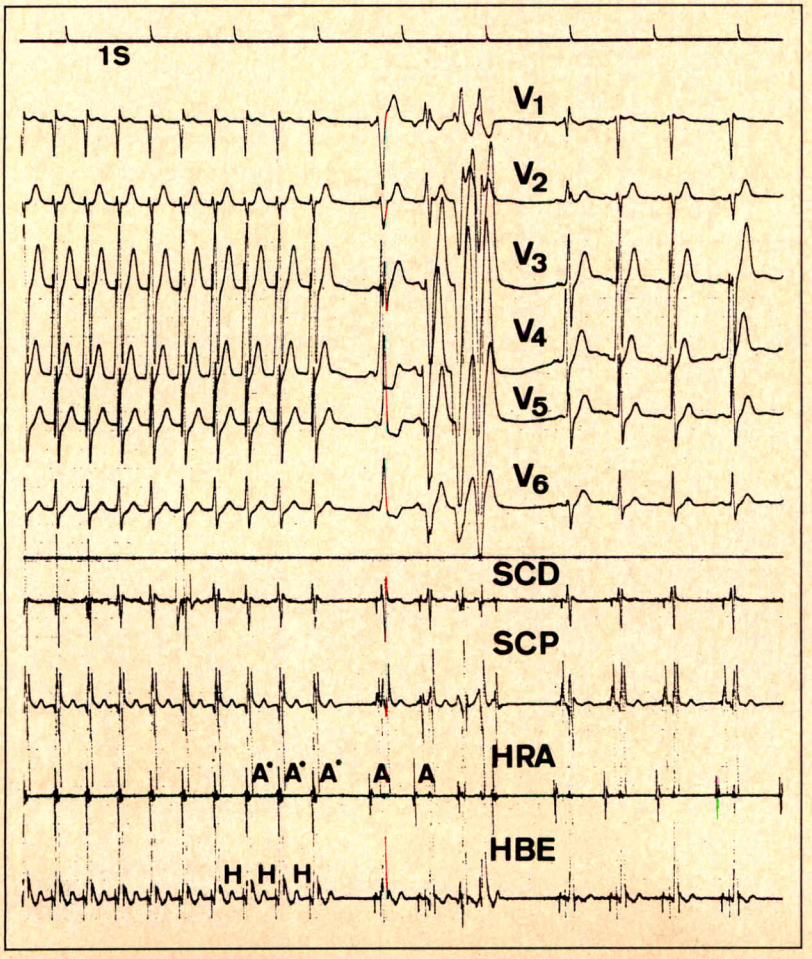


FIGURE 3. Tracing of the conversion of the induced tachycardia in a patient with Wolff-Parkinson-White syndrome and atrioventricular nodal tachycardia. The last complex of the tachycardia reveals retrograde atrial activation (A*), indicating anterograde block. The first QRS complex after conversion reveals a delta wave. Thereafter, 1 ventricular complex with right bundle branch block is followed by 2 ventricular premature beats, whereafter normal sinus rhythm resumes. HBE = His bundle electrogram; HRA = high right atrial electrogram; SCD = distal recording in the coronary sinus; SCP = proximal recording in the coronary sinus.

who received placebo. These adverse reactions were generally mild or moderate. Symptomatic hypotension was twice observed during sotalol, but several patients had systolic blood pressures that were persistently <90 mm Hg, particularly during sotalol administration. Only 1 episode of hypotension was reported as severe and necessitated discontinuation of the study drug (placebo). Four patients had short episodes of a new arrhythmia. These new rhythm disturbances were seen at the time of return to sinus rhythm in 3 patients receiving sotalol and in 1 patient receiving placebo. They were not considered important. The atrial fibrillation that was observed in 1 patient had already occurred during previous treatment with metoprolol.

DISCUSSION

Attacks of paroxysmal SVT are unpredictable.[12] Many patients have only brief and infrequent episodes. This makes preventive treatment often unacceptable, even if the arrhythmia is disabling. Therefore, termination of attacks is an important medical issue. Episodic treatment has been proposed for paroxysmal arrhythmias in general, and is widely accepted by patients and physicians.[13] As the AV node is a common pathway for AV nodal reentrant tachycardia and for circus movement tachycardia in patients with Wolff-Parkinson-White syndrome or a concealed bypass tract, most actions to terminate tachycardia are directed to delay or interrupt conduction in the AV node.

The autonomic nervous system plays an important role in the genesis and maintenance of arrhythmias in general, and of paroxysmal SVT in particular. Sinus and AV nodal tissue have an important autonomic innervation. Therefore, termination of paroxysmal SVT is usually attempted with vagal maneuvers. It has been reported that up to 80% of patients with AV nodal reentrant tachycardia convert to sinus rhythm with carotid sinus massage.[1,14] This figure is not accepted by other investigators, and it has been suggested that the Valsalva maneuver and breath-holding during facial immersion are more potent actions for the termination of tachycardia.[15] However, a considerable number of patients remain in tachycardia after such procedures, as it is known that a tachycardia is more difficult to terminate after the initial moments, when compensatory cardiovascular reflexes are established.[16] Therefore, an antiarrhythmic drug with additional β-blocking properties is very attractive.

Efficacy of intravenous sotalol for terminating reentrant supraventricular tachycardias: This is the first placebo-controlled, randomized study demonstrating that intravenously given sotalol is highly effective in terminating reentrant SVT. The rate of conversion in this study was 100% in patients with spontaneous and 73% in patients with induced SVT. This conversion rate is higher than was obtained with sotalol in earlier noncontrolled studies, performed in smaller numbers of patients. However, most investigators used small doses of sotalol (0.4 to 0.6 mg/kg).[11,17] Prakash et al[17] found 4 of 6 patients converting to normal sinus rhythm after the intravenous injection of 10 to 20 mg of sotalol. Higher dosages (1.5 mg/kg) reverted about 70% of patients with AV nodal reentrant tachycardia as well as with accessory pathways.[18,19] Even if SVT is not converted to normal sinus rhythm, sotalol decreases the ventricular rate after 2 minutes, compared with placebo. This is in accordance with data presented by other investigators, and occurs in both types of SVT.[10,19]

Site of termination of the tachycardia: In this study, the site of termination by sotalol was found to be predominantly the fast (retrograde) pathway for patients with AV nodal tachycardia, and the accessory pathway in the ventriculoatrial direction for the other patients. Similar findings in patients with accessory pathways have been reported.[9] These observations confirm the clearly different electrophysiologic properties of sotalol, compared with other β blockers, which exert their activity mainly by blocking the AV node in the anterograde direction.

Comparison with other agents: A conversion rate of 40% was reported after intravenous administration of practolol.[3] The additional (class III) activity of sotalol may explain its superiority in terminating SVT in comparison to pure β blockers. We do not yet have evidence that the class III effect plays an important role in the obtained result. D-sotalol, administered in comparable dosage, has a class III effect in humans. However, the only specific class III activity that can be related to termination of SVT is a change in the refractoriness of the atria.[20] Slowing of the ventricular rate is also observed with other β blockers.[10] For verapamil and diltiazem, figures of 95% are given.[3,21] The conversion rate found for sotalol in the dosage used for this study compares with the rate found for those drugs.[4] Other new antiarrhythmic agents, such as propafenone and adenosine triphosphate, are extremely effective for termination.[4,22] However, the limitations and adverse effects of adenosine triphosphate are well known.[2] Adenosine triphosphate is a short-acting drug, and it is not unusual to observe early recurrence of tachycardia after successful termination. Furthermore, it is widely accepted that class IC drugs can have important hemodynamic side effects during intravenous administration, at least in patients with impaired left ventricular function.[23]

Safety: The administration of sotalol is associated with a reduction in the ventricular rate and a mild de-

crease in systolic and diastolic blood pressures. However, the incidence of adverse reactions associated with the intravenous administration of sotalol was low. Reactions were transient and of mild to moderate severity. Hypotension and dizziness were observed, but it remains uncertain whether they are due to the arrhythmia or to the drug. The short arrhythmias during or after administration of sotalol occurred before or immediately after the termination of the SVT. Arrhythmias have also been reported to occur at the time of termination of SVT by vagal maneuvers and administration of verapamil.[24,25] It is thought that they are related to autonomic imbalance.

Clinical implications: In this study, sotalol appears to be effective and safe for the termination of reentrant SVT. Its efficacy in converting SVT to sinus rhythm is comparable to that of some calcium antagonists and adenosine. Calcium antagonists have several limitations, and caution is necessary if patients with hypotension or ventricular preexcitation, who are prone to atrial fibrillation, are treated. Sotalol acts on accessory pathways as well as on the AV node, and had only minor effects on the blood pressure of our patients. Therefore, sotalol can be considered a drug of choice for the acute termination of reentrant SVT.

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APPENDIX

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Monitoring and data handling: Bristol-Myers International Corporation (Brussels): D. Marvel, BSc, R. Gratton, PhD, J. Temmerman, PhD; Bristol-Myers International Corporation (Paris): B. Bregman, PhD.

Prediction of Uneventful Cardioversion and Maintenance of Sinus Rhythm from Direct-Current Electrical Cardioversion of Chronic Atrial Fibrillation and Flutter

Isabelle C. Van Gelder, MD, Harry J. Crijns, MD, Wiek H. Van Gilst, PhD, Remco Verwer, MD, and Kong I. Lie, MD

The present study was undertaken to reassess prospectively the immediate and long-term results of direct-current electrical cardioversion in chronic atrial fibrillation or atrial flutter, and to determine factors predicting clinical outcome of the arrhythmia after direct-current cardioversion. Two-hundred forty-six patients underwent direct-current electrical cardioversion and were followed during a mean of 260 days. Multivariate analysis was used to identify factors predicting short- and long-term arrhythmia outcome. Cardioversion was achieved in 70% of patients with atrial fibrillation and in 96% of patients with atrial flutter. Stepwise logistic regression analysis revealed that arrhythmia duration ($p < 0.001$), type of arrhythmia (fibrillation vs flutter, $p < 0.02$) and age ($p < 0.05$) independently influenced conversion rate. On an actuarial basis, 42 and 36% of patients remained in sinus rhythm during 1 and 2 years, respectively. Multivariate regression analysis revealed that the type of arrhythmia ($p = 0.0008$), low precardioversion functional class ($p = 0.002$) and the presence of nonrheumatic mitral valve disease ($p = 0.03$) independently increased the length of the arrhythmia-free episode. Rheumatic heart disease shortened this period ($p = 0.03$). In conclusion, patients having a high probability of conversion together with a prolonged post-shock arrhythmia-free episode can be identified. This may improve the cost-benefit ratio of cardioversion.

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Direct-current electrical cardioversion, introduced by Lown et al[1] in 1962, is reported to restore sinus rhythm in approximately 90% of patients with chronic atrial fibrillation and in 97% of patients with atrial flutter.[2] After cardioversion only 20 to 60% of patients maintain sinus rhythm during the first year, irrespective of the institution of prophylactic antiarrhythmic drug treatment.[3–13] Since the introduction of routine direct-current electrical cardioversion into clinical practice, many investigators have studied the factors determining the immediate and long-term outcomes of this intervention. However, the present population subjected to electrical cardioversion differs in various ways from those previously studied, because the diagnostic and therapeutic possibilities for arrhythmia-related conditions have changed drastically. Also, prevention of arrhythmia recurrence changed after the introduction of newer antiarrhythmic drugs. Although more recent studies[14,15] have reevaluated direct-current electrical cardioversion for chronic atrial fibrillation, they were designed on a small retrospective basis and multivariate analysis was not performed. The present study was undertaken to reassess prospectively the immediate and long-term results of direct-current electrical cardioversion in a large cohort of patients. With use of multivariate analysis, factors predicting the clinical outcome of the arrhythmia after cardioversion were determined.

METHODS

Study patients: Between February 1986 and June 1989, 302 consecutive patients with chronic atrial fibrillation or atrial flutter were referred for direct-current electrical cardioversion to our hospital. Fifty-six patients were excluded: 41% because of sinus rhythm at admission, 30% for unstable heart failure or cardiogenic shock and 20% because of the presence of a severe systemic disease. The remaining 9% were excluded for miscellaneous reasons (sick sinus syndrome without implanted pacemaker, acute myocardial infarction and contraindications to anticoagulant therapy). Two hun-

TABLE I Characteristics of 246 Patients Before Direct-Current Cardioversion

Age (yrs) (range)	60 ± 12* (25-86)
M/F (n)	137/109
Atrial fibrillation/flutter (n)	191/55
Underlying heart disease (%)	
Coronary artery disease	24
Rheumatic heart disease	24
Systemic hypertension	11
Congenital heart disease	6
Cardiomyopathy	10
Nonrheumatic valvular disease	8
Hyperthyroidism, corrected	2
Lone arrhythmia	15
Previous duration (mos)	
Mean	28 ± 45*
Median (range)	8 (0.04-300)
Previous episodes of fibrillation/flutter (n)	1.8 ± 2.0*
Total duration of arrhythmia (mos)	
Mean	52 ± 66*
Median (range)	24 (0.04-400)
NYHA class I/II/III/IV	84/97/62/3
Cardiac thoracic ratio (%)	53 ± 7*
Left atrial size (mm)	
Long axis	46 ± 8*
Apical view	68 ± 10*
Right atrial size, apical view (mm)	60 ± 8*
Left ventricular end-diastolic diameter (mm)	52 ± 9*
Left ventricular end-systolic diameter (mm)	37 ± 9*
Height of fibrillation wave in lead V_1 (mm)	1.3 ± 0.7*
Plasma potassium concentration (mmol/liter)†	4.3 ± 0.5*
Treated with diuretics/ACE inhibitors (n)	110/44

*Mean ± standard deviation.
†At the cardioversion.
ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

dred forty-six patients underwent direct-current electrical cardioversion. Patient characteristics are listed in Table I. The type of underlying heart disease was determined from patient history, physical examination, 12-lead electrocardiogram, chest x-ray, 2-dimensional echocardiogram, bicycle exercise test and, if available, coronary angiogram. In all patients, hyperthyroidism was excluded by using standard tests. Previous duration of the arrhythmia was determined by careful examination of the patient's medical record, by questioning the patient and by reviewing all previous electrocardiograms available.

Definitions: Chronic atrial fibrillation or flutter was defined as documented atrial fibrillation or flutter with a duration of >24 hours without intercurrent sinus rhythm. To validate this criterion, 24-hour ambulatory electrocardiograms were recorded before cardioversion. "Lone" atrial fibrillation or "lone" atrial flutter was defined as atrial fibrillation or flutter in the absence of any demonstrable underlying heart disease.[16] Previous arrhythmia duration was defined as the time from the onset of the last episode of arrhythmia to cardioversion. Total arrhythmia duration was defined as the complete arrhythmia history from the onset of attacks of documented atrial fibrillation or flutter. Successful cardioversion was defined as maintenance of stable sinus rhythm for >24 hours after cardioversion.

Direct-current electrical cardioversion and follow-up: All cardioversions were performed on an elective basis. Patients were receiving oral anticoagulant drugs >4 weeks before direct-current electrical cardioversion. Efficacy of anticoagulation, monitored by the regional thrombosis service on a regular basis, depended on the prothrombin time and was considered adequate if the prothrombin time was between 2.4 and 4.8 INR. Digitalis was withheld >5 days before direct-current electrical cardioversion. Calcium antagonists with a negative chronotropic action (verapamil and diltiazem) were discontinued >1 day before the cardioversion. All other drugs were continued. Patients with previous hyperthyroidism were cardioverted only 3 months after achievement of the euthyroid state.[17] Immediately before the cardioversion, serum electrolyte concentrations and the prothrombin time were determined. Cardioversion was not performed when the potassium concentration was <3.5 mmol/liter or the prothrombin time >4.8 INR. A 12-lead electrocardiogram was recorded to determine electrocardiographic intervals and the height of the fibrillation waves in lead V_1. A continuous drip infusion of 5% glucose was introduced. To cope with unexpected bradycardia or asystole, 0.5 mg of atropine, 0.4 mg% of isoprenaline for infusion and a transthoracic pacemaker (PACE AID, Cardiac Resuscitator, Portland, Oregon) were readily available. Direct-current electrical cardioversion was performed in the postabsorptive state during light general anesthesia using 20 mg of etomidate intravenously. Only before June 1988 was 0.05 to 0.1 mg of fentanyl given intravenously as premedication. During the whole procedure, an anesthesiologist was present. For cardioversion, we used a calibrated Hewlett Packard 78620-A defibrillator with hand-held paddle electrodes (11.4 × 11.4 cm), in combination with Littmann defibrillation pads. This defibrillator was capable of storing 400 J of energy. After March 1, 1988, we used a Hewlett Packard 43120-A defibrillator capable of a capacitor discharge of 360 J. One paddle electrode was placed right parasternally, in the anterior position; the other was placed in a lateral position, in the midaxillary line. According to the protocol, we started with 50 J of stored energy in patients with atrial fibrillation and with 30 J in patients with atrial flutter. The next step for patients with atrial flutter was a shock of 50 J. Thereafter, energy of subsequent shocks was doubled for both patients with atrial fibrillation and flutter. The procedure was ended after restoration of sinus rhythm or 2 attempts at the highest level of stored energy. The time between consequent shocks was between 1 and 1.5 minutes. After each attempt, continuous

rhythm recordings were obtained to determine the rhythm.

A 2-dimensional echocardiogram was recorded on the day of the electrical cardioversion. Right and left atrial dimensions as well as left ventricular dimensions were determined, according to the method of Feigenbaum.[18]

To assess early recurrences of the arrhythmia and arrhythmia complaints, patients were observed in the coronary care unit by using real-time monitoring during 24 hours. During this observation period, prophylactic antiarrhythmic drugs (except amiodarone) were instituted. Because of its long half-life, amiodarone was instituted before cardioversion for ≥1 month. Drug therapy was not randomly assigned and depended on the patient's arrhythmia history and whether the patient was qualified for 1 of the ongoing prophylactic drug trials in our department. Drugs used were quinidine, flecainide, disopyramide, sotalol and amiodarone. Most patients with a first paroxysm of the arrhythmia did not begin with antiarrhythmic therapy. Patients still in sinus rhythm were discharged after 24 hours of observation.

After discharge, patients were evaluated in the outpatient department after 1, 3 and 6 months and at 6-month intervals thereafter. Prophylactic antiarrhythmic drugs were discontinued only in case of recurrence or if drug-related adverse effects occurred.

End points: Primary end points were unsuccessful cardioversion and arrhythmia recurrence during follow-up.

Statistical analysis: Data are reported as mean ± standard deviation. Median values were used only in case of a nonparametric distribution of variables. Logistic regression analysis was performed with the success or failure of direct-current electrical cardioversion as the dependent variable and the clinical parameters, as listed in Table I, as the independent variables. This analysis was performed with use of SYSTAT biostatistic software. The logistic model was of the form: P (success cardioversion) = $\exp(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3)/1 + \exp(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3)$. Multivariate regression analysis (SPSS statistical package) was used to evaluate factors influencing the duration of arrhythmia-free days after successful direct-current electrical cardioversion, using the parameters listed in Table II. The model used was: arrhythmia-free episode after cardioversion (days) = $\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5$. Continuous variables were compared by using Student's *t* test for independent samples. The Wilcoxon test was used for categorical variables. A chi-square test or Fisher's exact test (for cells <5) was used to determine the 2-tailed statistical significance of associations in 2-by-2 tables. P values <0.05 were considered to indicate statistical significance.

TABLE II Characteristics of 186 Successfully Cardioverted Patients

Age (yrs) (range)	59 ± 13* (25–86)
M/F (n)	107/79
Atrial fibrillation/flutter (n)	133/53
Underlying heart disease (%)	
Coronary artery disease	24
Rheumatic heart disease	21
Systemic hypertension	9
Congenital heart disease	6
Cardiomyopathy	11
Nonrheumatic mitral disease	5
Nonrheumatic aortic disease	4
Hyperthyroidism	2
Lone arrhythmia	18
Previous duration (mos)	
Mean	16 ± 27*
Median (range)	6 (0.04-228)
Previous episodes of atrial fibrillation/flutter (n)	1.9 ± 2.2*
Total duration arrhythmia (mos)	
Mean	43 ± 60*
Median (range)	20 (0.4-400)
NYHA class I/II/III/IV (n)	66/75/43/2
Cardiac thoracic ratio (%)	53 ± 7*
Left atrial size (mm)	
Long axis	45 ± 8*
Apical view	67 ± 10*
Right atrial size, apical view (mm)	60 ± 7*
Left ventricular end-diastolic diameter (mm)	52 ± 9*
Left ventricular end-systolic diameter (mm)	37 ± 9*
Height of fibrillation wave in lead V_1 (mm)	1.4 ± 0.7*
Treated with F/S/D/A/Q/no drug (n)	70/9/2/15/7/83

*Mean ± standard deviation.
A = amiodarone; D = disopyramide; F = flecainide; NYHA = New York Heart Association; Q = quinidine; S = sotalol.

RESULTS

Immediate outcome of direct-current electrical cardioversion: A successful cardioversion with >24 hours maintenance of sinus rhythm was achieved in 70% of patients with atrial fibrillation and in 96% of patients with atrial flutter. For the whole group, cardioversion was effective in 76% of patients. Unstable sinus rhythm or atrial rhythm followed by an early recurrence (between 0.5 and 24 hours) was found in 10 patients (17% of all failures). In 13 patients, the arrhythmia recurred after only a few sinus beats.

The most important parameter related independently to the success or failure of direct-current electrical cardioversion was the duration of the last episode of atrial fibrillation or flutter before the cardioversion ($\beta_0 = -3.7$; estimate = 0.03; $p < 0.001$). Other parameters significantly related to successful cardioversion were atrial flutter (estimate = −2.3, $p < 0.02$) and age (estimate = 0.03, $p < 0.05$). All other parameters were not significantly related to outcome. For example, using the formula of the logistic regression analysis, the

chance of a successful cardioversion in a 40-year-old patient with atrial flutter for 1 month would be 99%; if he had atrial fibrillation, it would be 91%.

Follow-up: Table II lists all postcardioversion patients who were discharged in sinus rhythm. During follow-up, the mean ± standard deviation duration of sinus rhythm was 260 ± 309 days, with a range of 1 to 1,198 days. Figure 1 shows the actuarial percentage of patients free of arrhythmias during a follow-up of 2 years. Of all recurrences, 67% occurred within the first month. Factors significantly increasing the number of arrhythmia-free days were the presence of atrial flutter ($\beta_0 = 312$, coefficient = 159, $p = 0.0008$), a lower New York Heart Association classification for exercise tolerance (coefficient = −85, $p = 0.002$) and underlying nonrheumatic mitral valve disease (mitral valve prolapse or congenital mitral stenosis, coefficient = 205, $p = 0.03$). Presence of rheumatic heart disease significantly shortened the arrhythmia-free period after the cardioversion (coefficient = −119, $p = 0.03$). Other characteristics did not have a prognostic significance.

Death occurred in 10 patients after a mean follow-up of 208 ± 220 (range 1 to 599) days. Five patients died suddenly. Patient number 1 died suddenly 3 months after a successful cardioversion for his first episode of atrial fibrillation. This patient had low-grade aortic regurgitation with normal ventricular function. He did not have ventricular arrhythmia and was not treated with antiarrhythmic drugs. The cause of sudden death remained unclear. The second patient suffered from congestive heart failure due to a dilated cardiomyopathy. She was in stable sinus rhythm without antiarrhythmic therapy for 2 years after cardioversion. After an increase in the severity of heart failure, she died suddenly. Patient number 3 had hypertrophic cardiomyopathy without documented ventricular arrhythmias. He

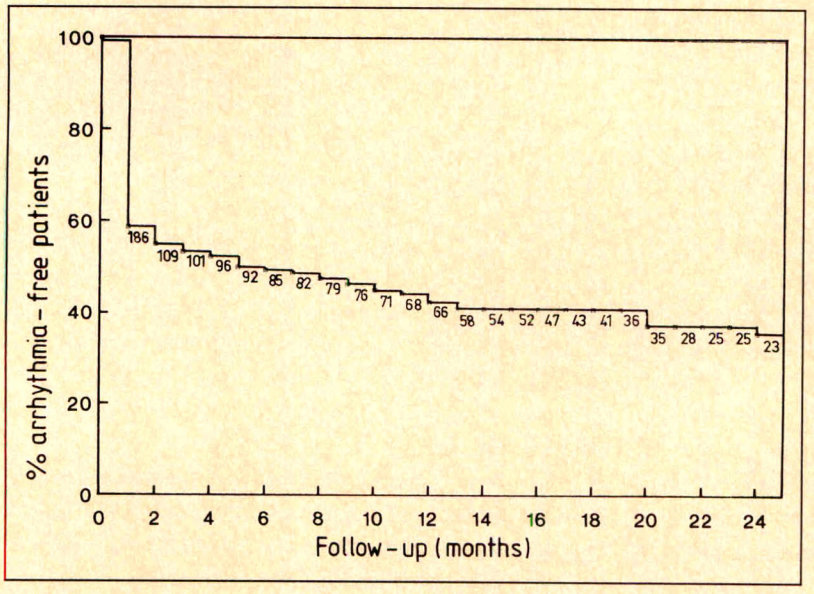


FIGURE 1. Percentage of patients free of arrhythmias calculated on an actuarial basis. *Numbers* indicate number of patients still evaluable at that moment (Mantel-Cox life-table analysis).

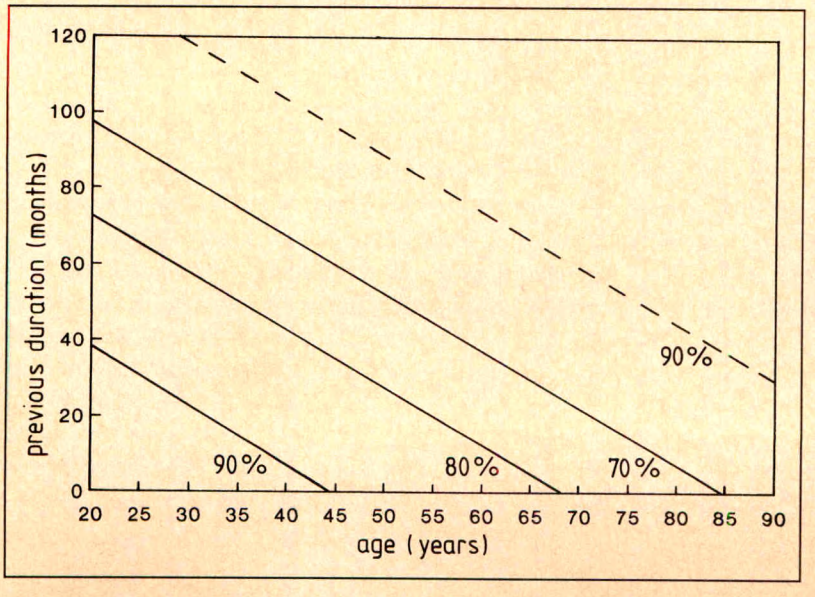


FIGURE 2. Percentiles showing the 70, 80 and 90% cardioversion rates for patients with atrial fibrillation *(solid lines)* and the 90% cardioversion rate for patients with atrial flutter *(dashed line)* in relation to previous arrhythmia duration and patient age.

died suddenly within 1 month after the shock. He was in sinus rhythm and not treated with antiarrhythmic drugs. The fourth patient died suddenly 3 months after a successful cardioversion for atrial fibrillation. This patient had undergone mitral valve replacement because of rheumatic mitral valve disease 10 months before the shock. She had normal left ventricular function, was not treated with antiarrhythmic drugs and did not have ventricular arrhythmias. The fifth patient died suddenly on the day of discharge from the hospital. During 1.5 years, this patient had been treated successfully with flecainide for recurrent sustained ventricular tachycardias late after a myocardial infarction. He underwent successful cardioversion for concomitant atrial flutter. Medication was not changed after the shock. The cause of sudden death remained unclear. The other 5 patients died during follow-up due to progressive congestive heart failure.

DISCUSSION

If a patient is presented for direct-current electrical cardioversion, there are 2 main questions. First, what is the probability of a successful cardioversion and, second, how long can sinus rhythm be maintained thereafter? Up to now no clinically useful decision algorithms, allowing for predictions concerning arrhythmia outcome, have been established. Estimations of probability of conversion and postcardioversion persistence of sinus rhythm may guide the clinician in the management of chronic atrial fibrillation or flutter. They may, for example, help to avoid highly unsuccessful cardioversions and might thereby improve the cost-benefit ratio.

This study showed that the type of underlying arrhythmia is a very important determinant of both short- and long-term arrhythmia prognosis. This means that in patients presenting with atrial flutter, cardioversion may be considered in almost all instances. This favorable arrhythmia prognosis is almost unaffected by other clinical parameters. However, in atrial fibrillation, arrhythmia outcome is highly influenced by several clinical factors. Our data suggest that the previous arrhythmia duration and the patient's age determine conversion rate, whereas functional class and type of underlying disease must be considered when estimating long-term maintenance of sinus rhythm. By taking these factors into account, calculations of short- and long-term outcomes may prevent unsuccessful cardioversions in patients with atrial fibrillation. The complexity of the formulas should not prevent the clinician from calculating arrhythmia outcome. The construction of curves giving percentiles for conversion might circumvent some of the arithmetic difficulties (Figure 2).

Multivariate analysis revealed that only a few patient characteristics determine arrhythmia outcome. In contrast to previous studies, left atrial diameters were not related to outcome. Also, other clinical parameters previously reported as significantly influencing arrhythmia prognosis could not be affirmed by the present study. Several explanations may be offered for these discrepancies. Most earlier studies did not use multivariate analysis, thereby potentially overestimating some predicting factors. In addition, only relatively small patient groups were investigated, leading to diminished sensitivity of the clinical characteristics studied. Finally, it is important to note that the durations of follow-up differ significantly between studies, with most follow-ups between only 3 and 6 months. However, the time of follow-up influences the rate of preserved sinus rhythm to some extent and may therefore affect the relation between clinical parameters and outcome.

After identification of the aforementioned parameters, multivariate analysis revealed that antiarrhythmic drugs did not further extend the number of arrhythmia-free days. This is in contrast with previously performed studies on quinidine, showing that quinidine is moderately effective.[3,4,12] However, in the present study, quinidine was only rarely used. The most frequently used drug was flecainide, which in a previously reported randomized trial appeared to be only modestly effective.[13] After failure of class I antiarrhythmic drugs, amiodarone may successfully prevent atrial fibrillation,[8–10] but amiodarone was also not extensively used. Finally, the absence of a significant effect of antiarrhythmics in the present study may also be explained by the fact that drug treatment was not randomized. Instead, in most cases, medical treatment was instituted on the basis of arrhythmia history and the number of medications used before study inclusion. As a consequence, antiarrhythmic drugs were mostly given to a subgroup of refractory patients, which may have caused a seeming lack of drug effect.

After the onset of atrial fibrillation, the mortality rate increases significantly.[19–22] In this study, 5 relatively young patients (2%) died suddenly. Previous studies have shown a higher incidence of shock-related deaths, but these were associated with the use of digitalis or quinidine.[23,24] Unfortunately, the causes of sudden death in the present study remained unclear. Although antiarrhythmic drugs have been associated with postcardioversion deaths,[12] in this study all cases of sudden death occurring late after the cardioversion were unrelated to the use of antiarrhythmic drugs. Only in the postinfarction patient with early post-shock sudden death did an arrhythmogenic effect of flecainide seem likely.[25]

The 24-hour success rate of direct-current electrical cardioversion was 76%. In patients with atrial fibrillation, it was 70%, which is low compared with earlier studies.[2,26–30] However, in previous studies, establishment of sinus rhythm immediately after the shock was

considered a successful cardioversion. If we had used this definition and not the 24-hour criterion, the success rate in atrial fibrillation would have been 74%. In addition, considering the clinical characteristics (Table I), the study patients should be characterized as difficult to treat with electrical cardioversion. Finally, patients were not pretreated with antiarrhythmic drugs. Such pretreatment might have improved cardioversion outcome.[31]

In our opinion, the 24-hour criterion used in the definition for successful cardioversion is relevant because of its consequences in clinical practice. During this period, patients are observed in hospital. If necessary, prophylactic antiarrhythmic treatment is instituted and the effect of this intervention may be monitored. Especially for initiation of drugs prolonging the duration of the action potential with potential induction of torsades de pointes, this is a safe way to go.[32] In case of an arrhythmia recurrence within this time period, a recardioversion may be performed during the same admission. Moreover, eventually late sequelae of the anesthesia can be treated adequately.

In contrast to previous reports,[19,20,26,27] patients with "lone" arrhythmia appeared to have the same arrhythmia prognosis as those with an underlying disease. Presumably, newer diagnostic possibilities used nowadays may have enabled better recognition of "lone" arrhythmia. Considering these facts, the same antiarrhythmic strategy as used in patients with underlying heart disease should be followed.

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Clinical and Angiographic Observations on Resuscitated Victims of Exercise-Related Sudden Ischemic Death

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The clinical and angiographic findings of 17 resuscitated victims of exercise-related sudden ischemic death are reported in an attempt to elucidate the mechanism(s) of these deaths. Ten survivors developed cardiac arrest during or after sporting activities (group A) and 7 others during or after an exercise stress test (group B). There were 15 men and 2 women. The mean age of group A was 46 years and of group B 55 years. Coronary risk factors, as well as previous angina and myocardial infarction, were more frequent in group B. Only 3 of the 17 survivors had anginal symptoms before sudden death. Sudden death in group A was associated with acute myocardial infarction in 8 and unstable angina in 2 and was associated in group B with acute myocardial infarction in 2, unstable angina in 3 and silent ischemia in 2. Coronary angiography was acutely performed in 15 patients. In most patients the ischemia-related coronary artery was totally or subtotally occluded. Clinical and angiographic findings indicate that exercise-related sudden ischemic death was due to an acute coronary event—in most cases unexpected and unpredictable. It is suggested that exercise-induced intracoronary changes were probably responsible for the development of acute coronary (sub)occlusion and sudden death.

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Numerous pathologic studies have shown that sudden death in subjects >40 years old is mainly associated with coronary artery disease.[1–3] Therefore, myocardial ischemia is believed to be essential in precipitating most episodes of sudden death. Physical exercise has been indicated as a contributing factor in the occurrence of a relevant number of sudden deaths.[4–6] The current opinion is that subjects prone to developing exercise-related sudden death have either known or unknown preexistent important coronary artery disease.[7–15] The precise pathophysiologic aspects of these cardiac arrests still remain uncertain.[16–18] Furthermore, exercise-related sudden death very often occurs unexpectedly and without prior warning symptoms in previously healthy subjects. This study attempts to elucidate the mechanism(s) of exercise-related sudden ischemic death.

METHODS

Patients: The study population comprised 17 patients, resuscitated victims of cardiac arrest. Ten patients (group A) survived out-of-hospital sudden death related to sporting activities and 7 patients (group B) were resuscitated from sudden death occurring during or after an exercise stress test. All but 1 of group A patients had neither a medical history nor symptoms suggestive of angina pectoris. All group A patients were well-conditioned, habitually sportive subjects. In group B, 5 of 7 patients had a history of angina or myocardial infarction. The patients underwent exercise stress testing for screening of cardiac disease (n = 2), evaluation of anginal complaints (n = 2), or routine control of ischemia >1 month after myocardial infarction (n = 3). Coronary risk factors in group A patients were cigarette smoking in 5 and hypertension (diastolic blood pressure >90 mm Hg) in 1; in group B patients, they were cigarette smoking in 5 and hypercholesterolemia (>240 mg/dl) in 2. Sudden death occurred in group A patients during sport in 6 and after sport in 4. In group B patients, sudden death occurred during the exercise test in 1 and thereafter in 6.

Definitions: Myocardial ischemia detected on the electrocardiogram was defined as ≥1 mm ST-segment elevation or depression in ≥3 contiguous leads.[19] Unstable angina was diagnosed when myocardial isch-

emia, lasting >15 minutes, was relieved at least temporarily after intravenous administration of nitroglycerin and was not associated with an increase in serum creatine kinase MB fractions. The diagnosis of acute myocardial infarction was made when myocardial ischemia lasted >30 minutes and persisted after intravenous administration of nitroglycerin, together with an increase in serum creatine kinase MB fractions and either with or without development of new Q waves on the electrocardiogram. Silent or asymptomatic myocardial ischemia was diagnosed as electrocardiographically detected ischemia lasting for ≥1 minute in conscious patients without an increase in serum creatine kinase MB fractions. Sudden ischemic death was defined as being unexpected witnessed death heralded by cardiocirculatory and respiratory arrest that occurred during or within 1 hour after physical exertion, related to electrocardiographically detected myocardial ischemia. Resuscitated victims (survivors) of sudden death were patients in whom cardiopulmonary resuscitation with or without medical or electrical intervention, or both, reestablished cardiac activity and circulation.

Procedures: The exercise stress test was performed on an upright bicycle ergometer, using a modified Bruce protocol.[20] A 12-lead electrocardiogram was continuously monitored during the test and up to 4 minutes after it. Blood pressure was measured every 2 minutes during and after the test and at maximal exercise tolerance. After informed consent was received from patients or their relatives, coronary angiography was performed in patients with acute myocardial infarction within 90 minutes and in patients with unstable angina within 3 hours after resuscitation, but was delayed (within 3 days) in patients with silent ischemia. Selective coronary and left ventricular angiography was performed using standard techniques. The left and right coronary arteries were visualized in ≥2 different views. Quantitative determination of coronary stenosis was made by comparing the stenotic segment with an adjacent normal segment proximal and distal to the lesion. The degree of collateral filling of an occluded coronary artery by ipsilateral or contralateral collateral vessels was determined according to the classification of Cohen et al[21] (from grade 0 [no collateral vessels] to grade III [complete filling of the vessel]). All electrocardiograms and coronary angiograms were blindly reviewed by 3 experienced cardiologists. The ischemia-related coronary artery was identified when the ischemic localization on the electrocardiogram corresponded with the anatomic region that was shown to be supplied by a (severely) diseased coronary artery.

RESULTS

Patient data: The arrhythmia monitored at resuscitation for group A was ventricular fibrillation in 8, asystole in 1 and undetermined in 1; for group B, it was ventricular fibrillation in 3, ventricular tachycardia or flutter in 3 and asystole in 1. In group A patients, sudden death occurred during or after sport without symptoms in 8 and preceded by anginal complaints a few minutes before collapse in 2. Symptoms or cardiac arrest, or both, occurred in 4 patients, 20 to 45 minutes after the end of sporting activities. After resuscitation, 8 patients were shown to have acute myocardial infarction, whereas 2 presented with unstable angina. In group B sudden death occurred with directly preceding anginal complaints in 2 patients with out-of-hospital cardiac arrest who were shown to have acute myocardial infarction after resuscitation, 60 and 45 minutes, respectively, after a normal exercise test. Three patients collapsed shortly (3 and 4 minutes) after a normal exercise test, but developed unstable angina after resuscitation. Two patients had silent ischemia before cardiac arrest occurred, but there was no evidence of ischemia on the electrocardiogram after resuscitation. The ischemic localization on the electrocardiogram corresponded in all cases with obstruction or occlusion of the expected ischemia-related coronary artery.

Angiographic data: The coronary angiographic findings of group A and B patients in relation to diagnosis and electrocardiographic changes during and after exercise testing are listed in Table I. GROUP A: At coronary angiography, all coronary arteries were occluded, except in 2 patients whose arteries were patent after intravenous administration of streptokinase before angiography. In these 2, reperfusion most probably occurred before catheterization, as suggested by the normalization of the ST segments on the electrocardiogram after streptokinase therapy. In the 2 patients with unstable angina, the coronary artery was occluded but filled by collateral supply. Associated coronary artery disease was present in 2 patients, 1 of whom had previously had a small myocardial infarction. Reperfusion and revascularization were successfully performed in all but 2 patients (nos. 5 and 6). One (no. 5), who had an occluded, collaterally filled coronary artery, was treated with a β blocker. One to 2 months after resuscitation, a symptom-limited exercise stress test was normal in all patients. GROUP B: No abnormal responses were observed during the exercise test in all but 2 patients who had ischemia on the electrocardiogram without anginal complaints. At coronary angiography, 2 patients with acute myocardial infarction (nos. 1 and 2) had occlusion of the infarct-related coronary artery. In the patient with partial collateral filling of the occluded artery, attempts to reperfuse the vessel were unsuccessful. This patient had a positive exercise test 3 months later. Of 3 patients who developed unstable angina (nos. 3 to 5), 2 had severe stenosis and 1 an occlusion of the ischemia-related coronary artery. In the latter, the artery

TABLE I Electrocardiographic and Coronary Angiographic Data of Survivors of Sudden Ischemic Death Related to Sport (group A) and to Exercise Testing (group B)

Pt. No.	ET ECG	PCPR ECG	Diagnosis	IRCA	% of Stenosis	ACD	Previous AMI
			Group A				
1	—	ST ↑ A	UA	LAD	100†	Right 100%	I
2	—	ST ↑ A	UA	LAD	100†	0	0
3	—	ST ↑ A	AMI	LAD	100	0	0
4	—	ST ↑ A	AMI	LAD	100	0	0
5	—	ST ↓ A	AMI	LC	100†	0	0
6	—	ST ↑ A	AMI	LAD	40*	0	0
7	—	ST ↑ A	AMI	Right	95*	0	0
8	—	ST ↑ A	AMI	LAD	100	0	0
9	—	ST ↓ A	AMI	LC	100	LAD 50%	0
10	—	ST ↑ A	AMI	Right	100	0	0
			Group B				
1	N	ST ↑ A	AMI	LAD	100	Right 30%	0
2	N	ST ↑ A	AMI	LAD	100‡	Right 40%	0
3	N	ST ↓ A–I	UA	IM	90	0	0
4	N	ST ↓ A–I	UA	IM	99	LAD 80%, right 50%	A
5	N	ST ↑ I	UA	Right	100†	0	I
6	ST ↓ L	N	SI	OM	99†	Right 50%	I
7	ST ↑ I	N	SI	Right	100†	0	0

*After streptokinase therapy.
†Completely and ‡partially filled by collateral flow.
A = anterior; ACD = associated coronary disease; AMI = acute myocarcial infarction; ECG = electrocardiogram; ET = exercise testing; I = inferior; IM = intermediate artery; IRCA = ischemia-related coronary artery; L = lateral; LAD = left anterior descending artery; LC = left circumflex artery; N = normal; OM = obtuse marginal artery; PCPR = postcardiopulmonary resuscitation; SI = silent ischemia; ST ↑ and ↓ = ST-segment elevation and depression; UA = unstable angina.

was filled by collateral supply. Of the 2 patients with asymptomatic ischemia (nos. 6 and 7), 1 collapsed at almost maximal predicted exercise tolerance, while the other collapsed during the recovery period after further increase of asymptomatic ischemia. In both cases, there were no signs of ischemia on the electrocardiogram after resuscitation. One patient had subtotal occlusion and the other total occlusion of the coronary artery involved. There was complete collateral filling of both vessels. Three patients (nos. 1, 3 and 4) underwent reperfusion of the ischemia-related coronary artery, while the other patients were treated with a β blocker. One to 3 months after resuscitation, all but 1 patient (no. 2) had a repeat normal exercise test. The distribution of (sub)occluded arteries was similar in both groups of patients, with sudden death occurring either during or after exertion. In both groups, left ventricular angiographic study revealed localized hypokinesia or akinesia corresponding to the infarct- or ischemia-related coronary artery. There were no ventricular abnormalities related to the culprit coronary artery in 4 patients with unstable angina and in the 2 patients with silent ischemia. There were no complications associated with the performance of coronary and left ventricular angiographic studies in any patients.

DISCUSSION

A considerable percentage (varying from 10 to 60%) of all sudden deaths has been reported as occurring during or after moderate and high-level physical activity.[6–9] In people aged >30 years, exercise-related sudden death is generally associated with 1- or multiple-vessel coronary artery disease and frequently also with myocardial scars.[1–6] Pathological examination of the coronary arteries revealed either fresh subocclusive thrombi or acute intimal lesions in 15 to 80% of cases.[1–15] However, acute coronary angiographic studies in this setting are lacking[22] and the pathophysiology of exercise-related sudden death remains speculative.[18] The present study shows that exercise-related sudden death can be caused by an acute coronary event that clinically can present as unstable angina, acute myocardial infarction and transient silent ischemia. The 2 groups of patients studied had in common the unexpected development of sudden death related to physical exertion. Furthermore, clinical and electrocardiographic data of patients having an exercise test provided information helpful in understanding the mechanism of these deaths.

With regard to sudden death associated with unstable angina and acute myocardial infarction, the patients undergoing the exercise test did not have ischemia and had no complaints. After the test there was a time delay before the development of ischemia, symptoms and sudden death. In the victims of sudden death related to sport, when symptoms occurred, either during or after sport, they ensued just before the development of cardiac arrest. The question relevant to the pathophysiology is how to explain the unexpected onset of symptoms or sudden death, or both. The finding of ischemia after resuscitation following a normal exercise test indicates that the onset of symptoms or sudden death, or both,

were due to sudden (sub)total impairment of coronary flow. Acute coronary angiography in patients with unstable angina and acute myocardial infarction confirmed this expectation. Exercise can provoke active vasomotion of diseased coronary arteries with activation of platelet aggregation and impairment of coronary flow.[23,24] It can also be hypothesized that active repeated coronary spasm during exercise can provoke fissuring or rupture of atherosclerotic plaques, leading to coronary (sub)occlusion by intraintimal hemorrhage or intracoronary thrombus formation, or both.[22,25,26] Recently, exercise-induced plaque rupture was suggested as the mechanism of coronary (sub)occlusion after a normal exercise test in 4 patients with previously normal or moderately narrowed coronary arteries.[27] Although silent ischemia is a usual finding in survivors of sudden death, life-threatening ventricular arrhythmias rarely occur during exercise testing.[28–30] Cardiac arrest was related to exercise-induced silent ischemia in 2 of our patients. The disappearance of ischemia after resuscitation implied restoration of myocardial perfusion. Their angiographic findings suggest that acute silent ischemia and cardiac arrest occurred as a result of acute coronary (sub)occlusion. The collateral filling of the vessels avoided myocardial damage, restored myocardial function and relieved ischemia on the electrocardiogram. The clinical and angiographic findings of the resuscitated victims of this study suggest that exercise itself unexpectedly induced intracoronary changes responsible for coronary (sub)occlusion. The observations of this study are limited by the lack of a control group of survivors of sudden death unrelated to exercise. Furthermore, no electrophysiologic study was performed to exclude enhanced electrical instability.

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Left Ventricular Diastolic Filling Alterations in Normotensive Young Adults with a Family History of Systemic Hypertension

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To characterize the cardiovascular consequences of a history of hypertension in first-degree relatives in normotensive young adults, 72 normotensive (diastolic blood pressure [BP] <90 mm Hg) healthy volunteers (age 18 to 30 years) were studied with 2 dimensionally guided M-mode echocardiography, pulsed Doppler echocardiography, and 2-hour automated BP monitoring. Of the 72 subjects, 19 (12 men and 7 women) had a family history of hypertension and were compared with 19 subjects without a family history of hypertension who were matched for systolic BP and gender. There were no detectable differences in 2-hour average BP, left ventricular (LV) mass or wall thickness, or echocardiographic systolic functional indexes between subjects with and without a family history of hypertension. Doppler-derived diastolic functional indexes demonstrated more prominent late diastolic filling in subjects with a family history of hypertension. Late diastolic transmitral flow time and flow velocity integral were greater (132 ± 24 vs 117 ± 17 ms, p <0.05; and 2.5 ± 0.7 vs 1.9 ± 0.5 cm, p <0.01, respectively). To measure possible gender-related effects of a family history of hypertension, the men and women were analyzed separately. The 12 men with a family history of hypertension had greater peak late (40 ± 0.9 vs 31 ± 0.8 cm/s, p <0.02) and ratio of late-to-early (0.64 ± 0.19 vs 0.46 ± 0.10, p <0.01) transmitral flow velocities and greater late transmitral flow velocity integrals (2.6 ± 0.8 vs 1.9 ± 0.5 cm, p <0.05) than the matched male control subjects. In contrast to the men, the female groups differed only in a longer late diastolic flow time in subjects with a family history of hypertension (129 ± 11 vs 109 ± 20 ms, p <0.05). The minimal findings in the women with a family history of hypertension may be a reflection of the later age of onset of hypertension and its related cardiovascular changes. Thus, in young normotensive men with a family history of hypertension, LV diastolic filling, while still normal, shifted toward the pattern of LV filling observed in hypertensive patients. These findings may represent very early, possibly inherited, characteristics of the hypertension syndrome.

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Left ventricular (LV) hypertrophy,[1–3] altered LV systolic function[2,4] and altered diastolic filling[4] have been demonstrated in patients with established hypertension. Increases in LV wall thickness can be found in patients with only borderline elevations of blood pressure (BP),[2] indicating that LV changes can occur early in the course of hypertension. LV hypertrophy is an independent predictor of cardiovascular morbidity and mortality in patients with hypertension[5] and is associated with a worse prognosis than high BP alone. There has been much interest in identifying predictors of subsequent high BP and LV hypertrophy in young subjects who are as yet normotensive. The presence of a family history of hypertension is a strong predictor of the development of hypertension in normotensive young subjects.[6,7] Moreover, a family history of hypertension has been associated with changes in LV function[6–11] and wall thickness.[8,12,13] The full implications of a family history of hypertension in normotensive young subjects have yet to be fully characterized. This study assesses the relations between a family history of hypertension in a first-degree relative and echocardiographic indexes of cardiac structure and function in normotensive young adults.

METHODS

Study group: Seventy-two normotensive young adults were examined with 2-dimensional, M-mode and

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Doppler echocardiography, 12-lead electrocardiography and 2-hour automated BP monitoring. Of this group, 19 subjects (12 men and 7 women, mean age ± standard deviation 26 ± 3 years [range 18 to 30]) subjects reported a family history of hypertension in at least 1 of their parents. BP was not measured in the parents. To eliminate the influences of BP on cardiac structure and function, the subjects with a family history of hypertension were matched for level of systolic BP and gender with subjects without a family history of hypertension, making 2 matched study groups of 19 subjects each. All subjects were in good health; they were without known cardiac, pulmonary or renal disease; and all had normal 2-dimensional echocardiograms and electrocardiograms. To eliminate the effects of the circadian rhythmic changes in BP,[14] all subjects were studied between 8 A.M. and 12 P.M. Height and weight measurements were obtained and body surface area calculated. All subjects gave informed consent, which was approved by the Institutional Review Board.

Blood pressure: Previous studies have shown that the average BP values obtained during a 2-hour period are representative of the whole-day BP value.[15,16] Automated BP was measured by the oscillometric method (Dinamap model 8455.002) every 8 minutes during 2 hours. BP monitoring was performed while the subjects were supine after an initial 30-minute period of rest. In separate studies, we previously found close concordance between values obtained by the oscillometric method and simultaneous conventional mercury sphygmomanometer and intraarterial measurements.[17] Any automated reading which was >2 standard deviations from the mean value was excluded as artifactual.[14] Average automated 2-hour systolic, diastolic and mean BPs were calculated by averaging the measurements obtained throughout the 2-hour period. The initial BP reading and the 2-hour average BP were <140/90 mm Hg in all subjects.

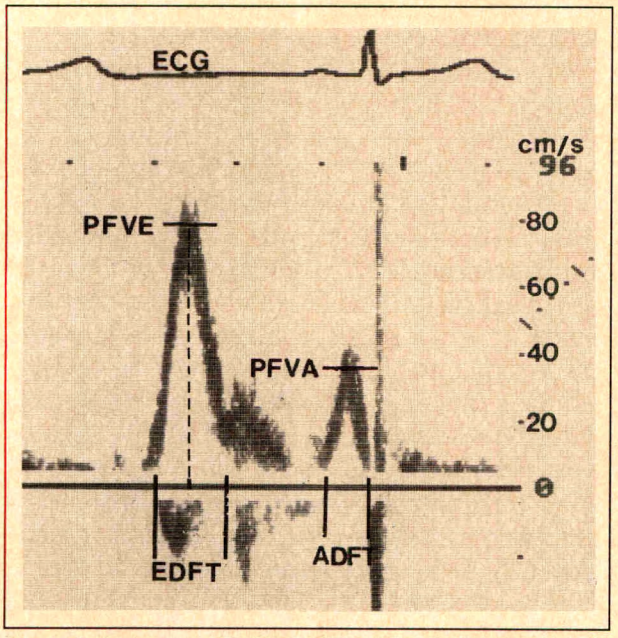


FIGURE 1. Transmitral Doppler flow velocities recorded from the apical 4-chamber view at the tips of the mitral valve demonstrating the measurements. See text for details. ADFT = late diastolic flow time; ECG = electrocardiogram; EDFT = early diastolic flow time; PFVA = peak late diastolic flow velocity; PFVE = peak early diastolic flow velocity.

Electrocardiography: Standard 12-lead electrocardiograms were obtained in the supine position with standard lead placement. The electrocardiograms were analyzed for the presence of LV hypertrophy by the Romhilt-Estes criteria.[18]

Echocardiography: M-mode and 2-dimensional echocardiography were performed from parasternal and apical windows. Standard views were obtained using a commercially available phased-array Doppler echocardiograph (General Electric, Pass II or RT500, Milwaukee, Wisconsin). Standard M-mode echocardiograms were recorded from the parasternal window on strip-chart paper at a speed of 50 mm/s. Measurements were obtained after the recommendations of the American Society of Echocardiography.[19] LV mass was calculated in grams with the equation: LV mass $= 1.05 \cdot [(LVDD + PW + VS)^3 - (LVDD)^3]$, where VS = ventricular septal thickness, LVDD = LV diastolic dimension, and PW = LV posterior wall thickness. Ejection fraction was calculated in percent by the equation: $(LVDD\text{-}LVSD)^3/(LVDD)^3$.

Doppler echocardiography: Transmitral flow velocities were recorded at the level of the mitral orifice from the apical window in either the apical long-axis or apical 4-chamber view as previously described.[20] Flow velocity was maximized by angulation in the lateral and orthogonal planes. No correction for the presumed direction of flow in the imaging plane was made. Spectral blood flow velocities were recorded on strip chart at a sweep speed of 50 mm/s.

Diastolic blood flow velocities and flow times were measured by the methods previously described.[20] Peak transmitral flow velocities were measured in centimeters per second, at the darkest point of the spectral wave forms (peak modal velocities) (Figure 1). The peak early diastolic flow velocity, corresponding to early rapid filling (PFVE), and peak late diastolic flow velocity, corresponding to atrial systole (PFVA), were measured in 3 to 5 cardiac cycles and the results averaged. Diastolic filling intervals were measured in milliseconds. Early diastolic flow time (EDFT) was measured from the onset of diastolic flow to the intersection of a line extrapolated to the baseline, and drawn through the darkest portion of the most rapid deceleration of the spectral wave form in early diastole. Late diastolic flow

TABLE I Clinical Characteristics of Study Participants

	With FHH (n = 19)	Without FHH (n = 19)
Age (years)	26 ± 3	26 ± 3
Height (cm)	171 ± 9	172 ± 8
Weight (kg)	64 ± 12	68 ± 9
BSA (m^2)	1.7 ± 0.2	1.8 ± 0.03
Systolic BP (mm Hg)	120 ± 11	119 ± 2
Diastolic BP (mm Hg)	74 ± 8	70 ± 2
Heart rate (beats/min)	63 ± 9	63 ± 12

BP = blood pressure; BSA = body surface area; FHH = family history of hypertension.

TABLE II Echocardiographic Characteristics of Study Participants

	With FHH (n = 19)	Without FHH (n = 19)
LV mass (g)	174 ± 47	187 ± 57
LV mass index (g/m^2)	99 ± 21	102 ± 24
Cardiac output (liters/min)	4.3 ± 1.5	5.1 ± 1.6
Stroke volume (ml)	70 ± 24	84 ± 31
Ejection fraction (%)	0.71 ± 0.05	0.68 ± 0.06
Total peripheral resistance (dynes · s · cm^{-5})	1,820 ± 657	1,465 ± 430

FHH = family history of hypertension; LV = left ventricular.

TABLE III Doppler Echocardiographic Characteristics of Study Participants

	With FHH (n = 19)	Without FHH (n = 19)
Peak early flow velocity (cm/s)	65 ± 14	68 ± 12
Peak late flow velocity (cm/s)	38 ± 8	33 ± 8
Late/early peak flow velocities	0.60 ± 0.17	0.50 ± 0.16
Early diastolic flow time (ms)	212 ± 32	201 ± 28
Late diastolic flow time (ms)	132 ± 24*	117 ± 17
Early diastolic flow velocity integral (cm)	6.9 ± 1.7	6.8 ± 1.2
Late diastolic flow velocity integral (cm)	2.5 ± 0.7†	1.9 ± 0.5

*$p < 0.05$; †$p < 0.01$.
FHH = family history of hypertension.

TABLE IV Doppler Echocardiographic Characteristics of Male Subjects

	With FHH (n = 12)	Without FHH (n = 12)
Peak early flow velocity (cm/s)	65 ± 14	69 ± 11
Peak late flow velocity (cm/s)	40 ± 9*	31 ± 8
Late/early peak flow velocities	0.64 ± 0.19†	0.46 ± 0.10
Early diastolic flow time (ms)	217 ± 37	192 ± 26
Late diastolic flow time (ms)	133 ± 30*	121 ± 14
Early diastolic flow velocity integral (cm)	7.0 ± 1.8	6.6 ± 1.4
Late diastolic flow velocity integral (cm)	2.6 ± 0.8*	1.9 ± 0.5

*$p < 0.05$; †$p < 0.01$.
FHH = family history of hypertension.

time (ADFT) was measured from the onset of late diastolic flow to the end of diastolic flow, determined by lines extrapolated to the baseline drawn through the steepest portion of the spectral wave forms (Figure 1).

Diastolic flow integrals were estimated in centimeters by the triangular assumption method.[20–22] Early diastolic flow velocity integral was approximated by the formula $PFVE \times 0.5 \times EDFT \times 10^{-3}$. Late diastolic flow velocity integral was approximated by the formula $PFVA \times 0.5 \times ADFT \times 10^{-3}$. The ratio of late to early peak LV filling velocities (A/E) was derived by dividing PFVA by PFVE.

Stroke volume (in milliliters) was calculated from the pulsed Doppler aortic systolic velocity integral (in centimeters) obtained from the LV outflow tract, and multiplied by the aortic anular cross-sectional area.[23] Cardiac output (CO) was calculated by multiplying stroke volume by heart rate. Total peripheral resistance (TPR) was calculated in dynes · s · cm^{-5} by the equation: $TPR = 80 \cdot MAP \cdot CO^{-1}$ where MAP = mean arterial pressure.

Statistical analysis: Cardiac structural and functional characteristics were compared between the 2 groups by unpaired Student's *t* tests with a commercially available statistical package (SPSS/PC+). Data are presented as mean ± standard deviation. A 2-tailed p value <0.05 was considered statistically significant. Multiple stepwise linear regression was used to test interactions between variables.

RESULTS

The anthropomorphic characteristics of the subjects with and without a family history of hypertension are listed in Table I. The groups had similar age, height, weight, systolic and diastolic BP, and heart rate. The cardiac structure and systolic function data are listed in Table II. Stroke volume, cardiac output, total peripheral resistance and ejection fraction were similar in both groups. LV mass, LV mass/body surface area and LV mass/height were similar in both groups. All but 4 subjects had a Romhilt-Estes point score of 0 and no subject had a score >4. Mean point score was similar in both groups, 0.4 ± 1.3 in subjects without and 0.2 ± 0.6 ($p = 0.52$) in those with a family history of hypertension. No subject had M-mode echocardiographic evidence of LV hypertrophy.

The Doppler transmitral LV filling data for the study group are listed in Table III. Doppler-derived diastolic functional indexes demonstrated more prominent late diastolic filling in subjects with a family history of hypertension. Late diastolic transmitral flow time and flow velocity integral were greater in subjects with than without a family history of hypertension. Stepwise multiple linear regression analysis failed to demonstrate any relation between LV filling indexes and LV mass, BP or heart rate.

To evaluate possible gender-related effects of a family history of hypertension, the men and women were

evaluated separately; the data are summarized for the male subjects in Table IV and individual data are presented in Figures 2 to 4. The 12 male subjects with a family history of hypertension had greater peak late diastolic flow velocities (Figure 2) and ratio of late to early peak LV filling velocities (Figure 3) than subjects without a family history of hypertension. Late transmitral flow velocity integral was also greater in the subjects with a family history of hypertension than the matched male control subjects (Figure 4). In contrast to the male subjects, the 2 female groups differed from each other only in a longer late diastolic flow time in those with than without a family history of hypertension (129 ± 11 vs 109 ± 20 ms, $p < 0.05$).

DISCUSSION

Although the mode of inheritance is not clear, subjects with a family history of hypertension have an increased likelihood of developing hypertension and potentially having target organ damage associated with hypertension. Other investigators have previously shown that a family history of hypertension is associated with exaggerated BP responses to submaximal[9] and isometric exercise[10] and also to mental stress.[24] We have previously demonstrated differences in cardiovascular function in young (mean age 13 years) normotensive adolescents with a family history of hypertension manifested by greater total peripheral resistance and BP reactivity than subjects without a family history of

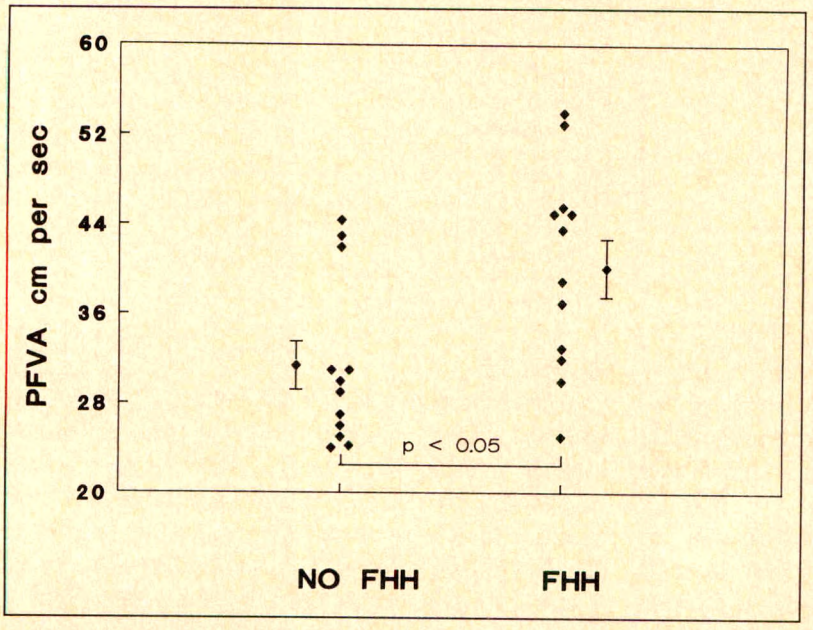


FIGURE 2. Individual patient data for peak late diastolic flow velocity (PFVA) in subjects with and without a family history of hypertension (FHH).

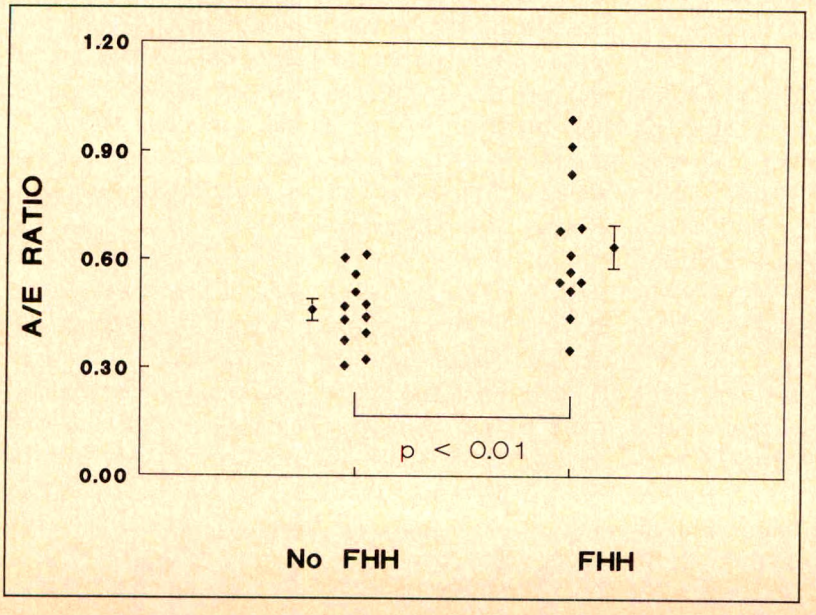


FIGURE 3. Individual patient data for the ratio of peak late to peak early diastolic flow velocities (A/E) in subjects with and without a family history of hypertension (FHH).

hypertension.[25] These findings, in the family history group, were similar to the cardiovascular characteristics found in young hypertensive patients[2] and suggest early cardiac involvement in an inherited hypertensive disorder that precedes the clinical appearance of high BP.

Diastolic filling alterations, characterized by a shift to greater late cycle filling, have been demonstrated in hypertensive patients[4,26–30] by echocardiographic, Doppler or nuclear scintigraphic techniques. Increases in peak late diastolic flow velocities and late to early peak LV filling velocity ratio have been observed in patients with mild to moderate hypertension when compared with normotensive controls.[11,27–30] The shift toward greater late diastolic LV filling in hypertensive patients is a reflection of altered diastolic LV function.

Our present findings that young adults with a family history of hypertension have a pattern of LV filling which, while still normal, is shifted toward that seen in hypertensive patients, suggests that cardiac changes associated with a family history of hypertension may occur before the appearance of documented elevations of BP. These findings occurred despite the complete absence of measurable changes in wall thickness or LV mass; indeed, these measurements in young subjects with a family history of hypertension tended to be slightly lower than the control subjects. Thus, the diastolic functional changes we found in the family history group appear to reflect intrinsic differences in the filling characteristics of the LV muscle, and cannot be attributed to hypertrophy-induced abnormalities.

Our findings, that there was no difference in LV wall thickness or muscle mass between subjects with or without a family history of hypertension, is of interest and differs from a recent report by others in which a family history of hypertension was associated with early evidence for hypertrophic changes in the left ventricle.[13] However, the average diastolic BP of the normotensive subjects in that study was 8 to 10 mm Hg higher than diastolic BP in the present study. This may be a meaningful difference in young persons with essentially normal BP and may account for the presence of some hypertrophic changes in their study.[13] This suggests that the subjects in the present study may be at an even earlier stage of the natural history of their hypertension and that alterations in LV diastolic function precede the development of hypertrophy.

In an earlier study,[20] we reported that alterations in LV diastolic filling may be associated with a tendency to higher, although not hypertensive, diastolic BP. The altered diastolic filling in that study was not associated with a family history of hypertension, but was linked to the presence of bimodal P waves in electrocardiographic lead V_1, which is possibly an early indicator of altered LV diastolic function. It is possible, therefore, that different mechanisms might contribute to changes in LV filling patterns: one type associated with a family history, and the other with early changes in BP itself. The present study eliminated the confounding effects of BP, however, by carefully matching subjects with and without family histories for their levels of systolic BP.

The relations of diastolic LV filling to heart rate and age are well established.[4,21,22] Neither of these relations were observed in the present study, presumably because we studied a small relatively homogeneous group of subjects within a narrow age range. The shift in LV filling toward the later part of diastole within the sub-

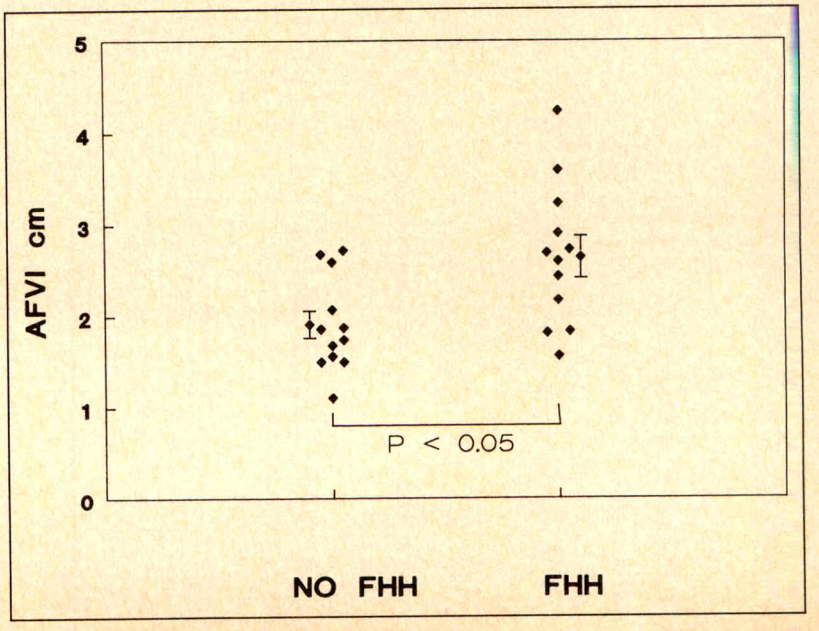


FIGURE 4. Individual patient data for late diastolic flow velocity integral (AFVI) in subjects with and without a family history of hypertension (FHH).

jects with a family history of hypertension was most pronounced in men. The absence of similar findings in women in this group is not readily explained. Further studies of concomitant factors that might mediate LV function are indicated.

LV outflow tract pulsed Doppler has been demonstrated to measure cardiac output accurately and reproducibly.[23] Cardiac output values obtained by this method correlate highly with thermal dilution values ($r = 0.93$). We found no differences in stroke volume or cardiac output between those with and without a family history, thus excluding these factors as explanations for the observed differences in LV filling.

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Left Ventricular Filling in the Systemic Hypertension of Obesity

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Cardiac structure and systolic as well as diastolic functions were evaluated by 2-dimensional M-mode echocardiography in lean and obese patients who were either hypertensive or normotensive. Diastolic function, as assessed by diminished normalized early peak filling rate and prolonged duration of rapid filling, was decreased in hypertensive patients compared with normotensive patients ($p = 0.02$). When compared with lean patients with similar blood pressure levels, obese patients exhibited a lower normalized peak filling rate ($p = 0.0014$) but no difference in duration of rapid filling. A significant correlation was observed between the normalized peak filling rate and either body mass index or left ventricular (LV) mass ($r = 0.355$ and $r = -0.32$, respectively; $p < 0.001$). Obese patients had greater LV end-diastolic and systolic dimensions ($p < 0.005$ and $p < 0.02$, respectively), LV wall thickness ($p < 0.05$) and LV mass ($p < 0.007$) than lean patients. Impairment of LV filling was most pronounced in obese hypertensive patients. It is concluded that the burden on the left ventricle imposed by obesity causes cardiac enlargement and impairment of LV filling regardless of levels of arterial pressure.

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Obesity and hypertension—2 disorders frequently coexisting in the same patient—are independent risk factors for cardiovascular disease.[1,2] Excess adipose tissue requires a higher cardiac output to provide for higher metabolic demands. Because of this, left ventricular (LV) stroke work is augmented in obesity, and LV end-diastolic pressure may become elevated.[3] This hemodynamic burden, when sustained, may cause structural cardiac adaptation and premature impairment of LV contractile function.[4–6] Alterations in LV structure and systolic performance have been described in morbidly obese patients, even in the absence of hypertension.[7–9] Conversely, a sustained elevation of arterial pressure can induce changes in cardiac anatomy and functions by mechanisms distinct from the ones in obese patients.[10–12]

No information is available regarding LV filling in normotensive or hypertensive obese subjects. The present study analyzes the effects of obesity and arterial hypertension on LV filling.

METHODS

Subjects: Thirteen obese normotensive and 41 obese patients with mild to moderate essential hypertension were matched for age, sex and mean arterial pressure with the same number of nonobese patients, either normotensive or hypertensive. Patients were considered to have established hypertension if their diastolic pressure was >90 mm Hg on repeated measurements with an appropriate size cuff in the outpatient clinic. Secondary causes for arterial hypertension were ruled out by routine clinical and laboratory examination as previously described.[13] All subjects had either never been treated or had discontinued taking all their medication ≥4 weeks before the study. Body mass index[14] (weight in kilograms divided by height in meters squared), a reliable measure of obesity, was used to classify the population into 2 groups: Nonobese subjects included 41 hypertensive and 13 normotensive subjects with a body mass index of ≤26 kg/m^2. Mildly to moderately obese subjects included the same number of patients with a body mass index >26 but <35 kg/m^2 (Table I). The protocol for the study was approved by our clinical investigation committee, and informed consent was obtained from each subject.

TABLE I Characteristics of the Studied Population

	Normotensive Subjects		Hypertensive Subjects	
	Lean (n = 13)	Obese (n = 13)	Lean (n = 41)	Obese (n = 41)
Age (years)	45 ± 3	49 ± 4	49 ± 2	49 ± 2
Men/women	8/5	8/5	26/15	26/15
White/black	11/2	11/2	10/31	11/30
Height (cm)	166 ± 1	168 ± 1	171 ± 2	169 ± 1
Weight (kg)	61 ± 3	87 ± 2*	71 ± 2	98 ± 2*
Body surface area (m^2)	1.67 ± 0.05	1.96 ± 0.03*	1.82 ± 0.03	2.07 ± 0.03*
Body mass index (kg/m^2)	22 ± 1	31 ± 1*	24 ± 1	34 ± 1*
Systolic pressure (mm Hg)	117 ± 3	122 ± 2	151 ± 3	155 ± 3
Diastolic pressure (mm Hg)	73 ± 2	76 ± 1	95 ± 2	95 ± 2
Mean arterial pressure (mm Hg)	88 ± 2	91 ± 2	113 ± 2	115 ± 2
Heart rate (beats/min)	70 ± 2	67 ± 3	71 ± 2	70 ± 2

*p <0.0001 (obese vs lean).
Hypertensive subjects were heavier and had higher body surface area than normotensive subjects (p <0.01).

TABLE II Left Ventricular Structure and Filling

	Normotensive		Hypertensive		Significance		
	Lean	Obese	Lean	Obese	H/N	O/L	Interaction
Septal thickness (cm)	0.9 ± 0.04	1.1 ± 0.02	1.2 ± 0.04	1.24 ± 0.04	<0.0001	<0.05	NS
Posterior wall thickness (cm)	0.83 ± 0.03	1.0 ± 0.02	1.02 ± 0.03	1.10 ± 0.04	<0.005	<0.005	NS
Diastolic dimension (cm)	4.5 ± 0.09	4.8 ± 0.09	4.5 ± 0.07	4.8 ± 0.08	NS	<0.005	NS
Systolic dimension (cm)	2.7 ± 0.06	2.7 ± 0.08	2.7 ± 0.06	3.0 ± 0.07	0.05	0.02	
Left ventricular mass (g)	135 ± 8	200 ± 6	220 ± 13	268 ± 20	<0.0001	0.005	0.69
Left ventricular mass index (g/m^2)	81 ± 4	102 ± 3	120 ± 6	128 ± 9	0.001	0.12	0.51
Peak filling rate (cm/s)	9.5 ± 0.3	8.2 ± 0.52	8.4 ± 0.4	7.4 ± 0.23	0.03	0.008	0.66
Normalized peak filling rate (1/s)	2.7 ± 0.11	2.2 ± 0.13	2.3 ± 0.13	1.9 ± 0.06	0.02	0.0014	0.53
Duration of rapid filling (ms)	225 ± 10	252 ± 28	274 ± 15	294 ± 14	0.02	0.22	NS

H/N = hypertensive/normotensive; NS = not significant; O/L = obese/lean.

Echocardiographic studies: A 2-dimensionally guided M-mode echocardiogram was recorded using a Toshiba SSA-60A ultrasonoscope interfaced with a line scan recorder (LSR-20B) and a probe of either PSB-25A 2.5 MHz or PSB-37A 3.75 MHz. Subjects were studied in the partial left decubitus position after a rest of ≥10 minutes until blood pressure and heart rate were stable. At the time the echocardiogram was recorded, blood pressure was determined by cuff sphygmomanometry, using phases 1 and 5 of the Korotkoff sounds. The LV echocardiogram was obtained in the standard manner at or just below the tips of the mitral valve leaflets, with the transducer applied in the third or fourth intercostal space. LV end-diastolic and end-systolic dimensions were measured at the peak of the R wave of the simultaneously recorded electrocardiogram and at the nadir of septal motion, respectively, according to the method of Friedman et al.[15] Wall thickness was measured following the Penn convention recommendations, which exclude the thickness of the endocardial echoes. Each echocardiographic tracing was coded and read in a blinded manner by 2 investigators. LV mass was calculated according to the formula of Devereux[16] and was also adjusted for body surface area. LV diastolic function was determined with computer assistance as has recently been described[17]: septal and posterior wall endocardial echoes were digitized, and continuous plots were generated of LV minor axis dimension versus time and the rate of change of dimension versus time. The early peak filling rate and the duration of rapid filling were derived. The peak filling rate was also normalized for the instantaneous LV dimension, and the duration of rapid filling was corrected for heart rate by dividing it by the RR interval. For each patient 3 to 5 consecutive cycles were analyzed and averaged. When interbeat variations exceeded 10%, 3 to 5 additional cycles were included in the analysis.

Statistics: Results were expressed as mean ± standard error of the mean. A 2-way analysis of variance was used to test differences between lean and obese subjects and patients with hypertension versus results in normotensive subjects. Subsequent pairwise tests between lean and obese subjects were performed within normotensive and hypertensive groups using Bonferroni's correction for p values. Pearson's correlation was

used to evaluate correlations between variables. Stepwise regression analysis was used to elucidate the main factors that determine ventricular filling.

RESULTS

Ventricular function: Compared with nonobese patients with similar arterial pressures, obese subjects had a lower ($p = 0.008$) and a normalized ($p = 0.0014$) peak filling rate. Peak filling rate, normalized peak filling rate and duration of rapid filling were impaired in hypertensive patients compared with normotensive subjects (Table II). Obese hypertensive patients had the lowest peak filling rate and normalized peak filling rate and the most prolonged duration of rapid filling.

A significant negative correlation was observed between the normalized peak filling rate and either body mass index or LV mass ($r = -0.355$ and $r = -0.32$, respectively, $p < 0.001$). Stepwise regression analysis testing age, mean arterial pressure, body mass index, LV mass and septal and posterior wall thickness as independent variables identified body mass index, LV mass and posterior wall thickness as the major determinants of normalized peak filling rate [$F(3.105) = 8.26$, $p < 0.05$].

Systolic function as assessed by ejection fraction, fractional fiber shortening and velocity of circumferential fiber shortening was slightly diminished in hypertensive patients compared with normotensive patients. Obese normotensive patients had systolic indexes similar to those of their nonobese counterparts, whereas obese hypertensive patients had a significantly lower ejection fraction and fractional fiber shortening than nonobese hypertensive patients.

Left ventricular structure: When compared with nonobese patients with similar arterial pressure, obese patients had significantly greater LV end-diastolic and end-systolic diameters (Table II). Posterior wall and septal thickness as well as LV mass were increased in the obese subject as previously reported.[4] LV diameters, septal and posterior wall thickness and LV mass were higher in hypertensive patients than in normotensive subjects (Table II).

DISCUSSION

The present study shows that LV filling, as reflected by normalized and peak filling rates, is diminished in obese subjects compared with nonobese subjects having similar levels of arterial pressure. These data expand and corroborate previous reports from our laboratory by Lavie et al,[18] identifying left atrial abnormalities in obesity, particularly in obesity hypertension. Diastolic filling abnormalities have been well documented in patients with arterial hypertension in whom the classic adaptation of the heart consists of concentric LV hypertrophy, i.e., an increase in wall thickness at the expense of chamber volume.[19,20] In contrast, the predominant cardiac adaptation in obesity consists of eccentric LV hypertrophy, i.e., thickening of the chamber wall and chamber dilatation.[4] Eccentric LV hypertrophy occurs as the classic adaptation to any volume overload such as is seen in anemia, valvular heart disease, arteriovenous shunting and obesity. Indeed, diastolic dysfunction has been described in some of these disorders that are characterized by a volume overload.[21–23] It seems most likely that our finding of impaired filling in obesity is an effect of the hypertrophy, per se (i.e., as ventricular wall thickens, it becomes less compliant). Conceivably, diastolic filling could additionally be impaired by myocardial ischemia,[24] which occurs often in LV hypertrophy.

LV filling was most impaired in patients with both obesity and hypertension. The heart of these patients has to carry the double burden of an increased preload as well as of an increased afterload. This double burden to the left ventricle, when sustained, is prone to lead to a rapid deterioration in systolic and diastolic cardiac function. Data from the Framingham cohort have documented that the risk of developing congestive heart failure increases along with the degree of obesity and that this increase is accelerated by the presence of arterial hypertension.[25]

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Effect of Bisoprolol on Blood Pressure and Arterial Hemodynamics in Systemic Hypertension

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Blood pressure, heart rate, common carotid and brachial arterial hemodynamics using pulsed Doppler flowmetry and pulse wave velocity determinations were evaluated using a double-blind crossover design versus placebo in 14 patients with sustained essential hypertension treated by the selective β_1 blocking agent bisoprolol. Blood pressure and heart rate significantly decreased after bisoprolol, whereas no significant change occurred in the diameter, the blood flow and in the vascular resistance of the carotid and brachial circulations. Pulse wave velocity significantly decreased in the brachioradial and the carotid femoral areas. The decrease in the latter was -1.6 ± 0.8 m/s with bisoprolol and -0.06 ± 0.80 m/s with placebo ($p = 0.001$). Brachial artery compliance significantly increased from 117 $\pm$ 49 to 205 $\pm$ 84 $cm^4 \cdot dynes^{-1} \cdot 10^9$ ($p = 0.001$), indicating that the antihypertensive effect of β_1 blockade is associated with an improvement in the viscoelastic properties of the brachial artery wall.

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Both clinical and experimental data[1,2] indicate that a nonselective β-blocking agent such as propranolol does not modify arterial compliance despite a significant blood pressure reduction. On the other hand, β-blocking agents with sympathomimetic activity have been shown to produce a slight increase in brachial artery diameter in hypertensive subjects.[3] Although such findings suggest that β-blocking drugs might have heterogeneous effects on the arterial system depending on their pharmacologic properties, no specific study was performed to investigate selective β blockade.

The selective β_1 blocking agent bisoprolol is known to have a high level of selectivity with a pharmacologic duration of action approximating 48 hours.[4,5] In the present, double-blind, crossover design, the effects of bisoprolol on the arterial system are studied in patients with sustained essential hypertension. Large arteries are investigated using noninvasive techniques involving pulsed Doppler flowmetry for the common carotid and the brachial arteries and determinations of pulse wave velocity.

METHODS

Patients: Fourteen patients with essential hypertension (7 men and 7 women, mean age $\pm$ 1 standard deviation 53 $\pm$ 8 years [range $\times$ 42 to 66]) completed this study. Mean weight and height were 73 $\pm$ 12 kg and 167 $\pm$ 9 cm, respectively. Diastolic pressure on mercury sphygmomanometer at the day of the inclusion was constantly >95 mm Hg after a 30-day placebo period. All subjects had mild to moderate hypertension according to World Health Organization criteria (90 mm Hg < diastolic blood pressure <115 mm Hg on mercury sphygmomanometer, Korotkoff phase V). Extensive clinical and biologic investigations were performed according to previously described procedures,[6,7] indicating that patients had essential hypertension with no cardiac, neurologic or renal involvement or arteriosclerosis obliterans of the legs, or diabetes mellitus. Patients gave written consent after a detailed description of the procedure.

The patients participated in an 8-week, randomized, double-blind, crossover study. After the placebo period, they were randomized into 2 groups. Subjects in group A received tablets containing 10 mg of bisoprolol daily

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for 4 weeks. Subjects in group B received identical tablets containing placebo. At the end of this period, a crossover was made with patients in group A taking placebo and in group B taking active treatment for 4 weeks. Hemodynamic determinations were performed at the day of the inclusion and at the end of the first (fourth week) and the second (eighth week) periods.

Hemodynamic determinations: The study was performed at controlled room temperature of 20 ± 2.5 C, after 30 minutes of rest, with the subject in the recumbent position. Hemodynamic measurements were obtained before and 5 hours after the last administration of bisoprolol or placebo (fourth and eighth week), according to the well-known pharmacokinetic and pharmacodynamic effects of the drug.[4,5] Arterial blood pressure was measured automatically every 2 minutes in the left arm with an oscillometric blood pressure recorder (Dinamap, model 845 P, Critikon, Tampa, Florida). Hemodynamic measurements were performed first on the right common carotid artery, then on the right brachial artery within 15 minutes, during which blood pressure remained stable. No significant changes in blood pressure and heart rate occurred when the 2 periods were compared.

Carotid and forearm hemodynamic values were obtained with a bidimensional pulsed Doppler system[7] (Alvar Electronics, Montreuil, France), the probe of which was fixed with a stereotactic device over the course of the artery as previously described and validated.[6,7] This apparatus enabled the diameter and the blood velocity of the artery to be measured according to 2 fundamental characteristics: a bidimensional recording of the Doppler signals and a range-gated time system of reception. The former was obtained with a probe containing 2 transducers, which formed a 120° angle between them, so that when Doppler signals recorded by each transducer were equal in absolute value, the ultrasonic incidence with the vessel axis was 60°. With the second characteristic, it was possible to select the length of delay from the emission and the duration of the reception and to convert this time echographically into the depth and the width of the Doppler measurement volume. Methodology and reproducibility have been described in detail elsewhere.[6,7] Blood flow was calculated as the product of the blood velocity and cross-sectional area deduced from the arterial diameter by using a cylindrical representation of the artery. Arterial blood flow was expressed in millimeters per minute. Local vascular resistance (mm Hg·min·ml^{-1}) was calculated as the ratio between simultaneous mean blood pressure and mean blood flow.

For the determination of pulse wave velocity, 5 different Doppler flow recordings were obtained simultaneously at 5 sites[6,8]: at the base of the neck over the common carotid artery, over the right femoral artery, over the right posterior tibial artery, over the right brachial artery in the axilla, and at the right radial artery at the wrist. Flow was measured with a nondirectional Doppler unit (SEGA M842 10 MHz) with handheld probes. Transcutaneous Doppler flow waves were recorded on a tape recorder at high speed (150 mm/s). Pulse wave velocity was determined as foot-to-foot wave velocity. The foot of the flow wave was identified as the point of the commencement at the sharp systolic upstroke. When this point could not be defined precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot wave was taken as the point of intersection of these 2 lines. The time delay was measured between the feet of the flow waves recorded at these different points and the electrocardiographic signal recorder simultaneously. The average of ≥10 beats was taken as pulse transit time. The distance travelled by the pulse was measured over the surface of the body with a tape measure as the distance between the different recording sites. Arterial pulse wave velocity was calculated as the ratio between distance and transit time. The reproducibility of the measurements have been published in detail elsewhere.[6,8]

Brachial artery compliance was evaluated using a propagative model.[6,8,9] For large arteries, the most widely accepted relation between pulse wave velocity (PWV) and elastic modulus (E)[8] is given by the Moens Koeteweg equation:

$$PWV^2 = (Eh/2rp)$$

or by the Bramwell-Hill equation:

$$PWV^2 = (VdP/dV)$$

where E = Young's modulus of the wall, h = wall thickness, r = vessel radius, p = blood density, dV,dP = changes in volume (V) and pressure. As detailed elsewhere,[9] assuming a thin arterial wall, compliance of the brachial artery (expressed per unit length) may be calculated as: $dV/dP = 3.14\ r^2/p\ PWV^2$.

Statistical evaluation[10]: Baseline values of groups A and B were compared with a 2-way analysis of variance and were not statistically different. Modifications of the different hemodynamic and biologic parameters were compared with a 3-way (patient, treatment, sequence) analysis of variance. This test did not indicate any difference in the 2 sequences of treatment. A p value <0.05 was considered significant.

RESULTS

Tables I, II and III summarize the mean value of blood pressure, heart rate, carotid and brachial arterial parameters and pulse wave velocity in the 3 conditions: baseline, after placebo and after active treatment.

After administration of bisoprolol, blood pressure and heart rate significantly decreased compared with placebo: systolic pressure, -17 ± 16 mm Hg (vs -6 ± 12 mm Hg; $p = 0.03$); diastolic pressure, -17 ± 12 mm Hg (vs -5 ± 10 mm Hg; $p = 0.006$); mean arterial pressure, -17 ± 13 mm Hg (vs -6 ± 11 mm Hg; $p = 0.01$). Similar changes were observed with heart rate: -20 ± 10 vs -4 ± 8 beats/min ($p = 0.0001$).

Significant changes in pulse wave velocity were observed after bisoprolol administration: -1.6 ± 0.8 vs -0.06 ± 0.80 m/s ($p = 0.001$) for carotid-femoral pulse wave velocity (Figure 1); -3.3 ± 2.4 m/s vs -0.3 ± 1.6 m/s ($p = 0.001$) for brachioradial pulse wave velocity; -1.3 ± 2.5 m/s vs -0.7 ± 1.6 m/s (difference not significant) for femorotibial pulse wave velocity.

No significant change in carotid and brachial hemodynamics were observed (Table II), except for brachial artery compliance which increased significantly after bisoprolol (205 ± 84 vs 117 ± 49 $cm^4 \cdot dynes^{-1} \cdot 10^{-9}$; $p = 0.001$) (Figure 2).

TABLE I Blood Pressure and Heart Rate

	Baseline	After Placebo	After Bisoprolol
Systolic blood pressure (mm Hg)	156 ± 15	148 ± 16	137 ± 18*
Diastolic blood pressure (mm Hg)	101 ± 5	94 ± 11	83 ± 12†
Mean blood pressure (mm Hg)	120 ± 7	112 ± 13	101 ± 14†
Heart rate (beats/min)	79 ± 12	77 ± 10	60 ± 11‡

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Values are mean ± 1 standard deviation.
The p value indicates the intergroup comparison between placebo and bisoprolol.

TABLE II Hemodynamic Parameters in Regional Circulations*

	Baseline	After Placebo	After Bisoprolol
Brachial artery			
Diameter (cm)	0.48 ± 0.06	0.47 ± 0.06	0.48 ± 0.05
Blood flow velocity (cm/s)	7 ± 4	6 ± 4	6 ± 2
Blood flow (ml/min)	81 ± 63	75 ± 55	64 ± 37
Resistance (mm Hg · min · ml^{-1})	2.4 ± 1.6	2.3 ± 1.3	2.1 ± 1.2
Common carotid artery			
Diameter (cm)	0.61 ± 0.07	0.61 ± 0.06	0.61 ± 0.07
Blood flow velocity (cm/s)	17 ± 5	18 ± 5	16 ± 5
Blood flow (ml/min)	303 ± 107	314 ± 100	289 ± 103
Resistance (mm Hg · min/ml^{-1})	0.47 ± 0.27	0.40 ± 0.17	0.41 ± 0.22

*No significant change was observed.
Values are mean ± 1 standard deviation.

DISCUSSION

In the present investigation, the β_1 blocking agent bisoprolol was shown to greatly decrease blood pressure in patients with sustained essential hypertension.

The antihypertensive effect of β-blocking agents is usually attributed to a decrease in vascular resistance at

TABLE III Pulse Wave Velocity Determinations

	Baseline	After Placebo	After Bisoprolol
Pulse wave velocity (m/s)			
Carotid femoral	9.5 ± 1.4	9.4 ± 1.3	7.9 ± 0.9*
Brachioradial	12.8 ± 2.3	12.6 ± 2.7	9.7 ± 2.0*
Femorotibial	12.8 ± 2.7	12.1 ± 2.5	11.5 ± 2.9

*$p < 0.001$.
Values are mean ± 1 standard deviation.

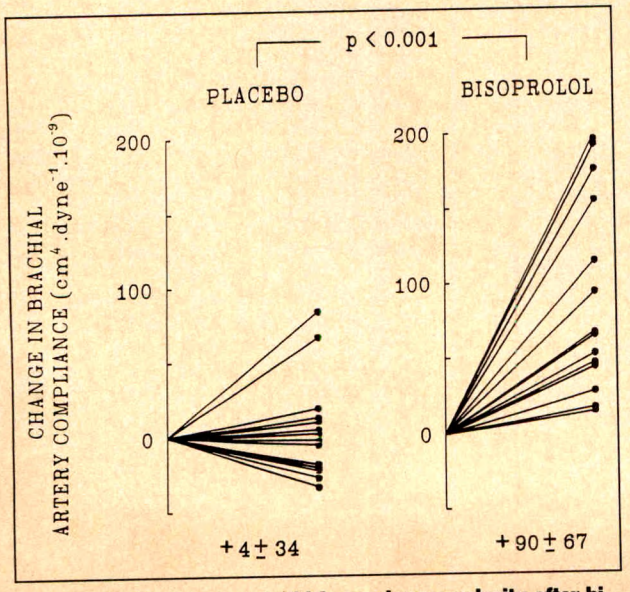


FIGURE 1. Changes in carotid femoral wave velocity after bisoprolol and placebo.

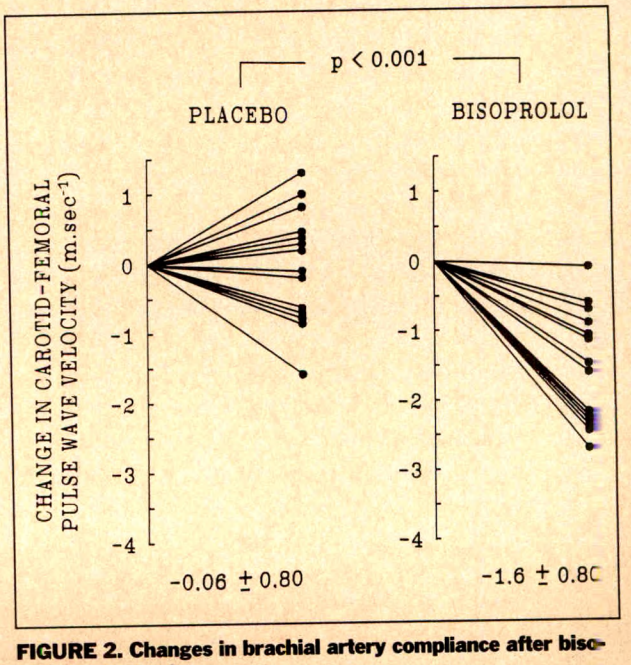


FIGURE 2. Changes in brachial artery compliance after bisoprolol and placebo.

any given value of cardiac output.[11] Because blood flow and vascular resistance were unchanged in the carotid and the brachial circulation after bisoprolol, the findings of our study support the hypothesis that arteriolar dilatation occurred in other regional circulations, as in the mesenteric or the renal areas.

Despite the significant reduction in blood pressure, there was no evidence of a passive change of the arterial diameter in the brachial and carotid circulation. Because blood flow velocity did not change, a flow-dependent mechanism could not explain the lack of change in arterial diameter.[12] Since diameter may be considered the same before and after blood pressure reduction, the result suggests that, after bisoprolol, a shift of the pressure-diameter curve occurred toward lower values in blood pressure.[9] However, the present pulsed Doppler method is known to have very precise limits for an adequate determination of internal diameter. The resolution of the method is directly related to the sample volume size and has been shown to approximate 0.035 cm.[7,13] In that condition, minor changes in arterial diameter may be present but remain outside the resolution limits of the method. This possibility appears likely with bisoprolol. Acute β_1 blockade by atenolol has been shown to cause a decrease in brachial artery diameter[14] and long-term bisoprolol to produce a decrease in abdominal aorta diameter[5] in patients with sustained essential hypertension. Since these drugs act on β_1 receptors with no effect on β_2 receptors, such findings may be attributed to the mechanical effect of the blood pressure reduction itself.

In contrast to the unchanged arterial diameter, bisoprolol produced a decrease in pulse wave velocity in the aortic, the brachioradial and the femorotibial areas. Only the changes observed in the aorta and the upper limbs were shown to be significant. Similar results have been observed with another β_1 blocking agent atenolol,[15] but not with metoprolol.[16] Reasons for this discrepancy are difficult to explain. More significant changes may be observed with crossover designs (as for atenolol and for our study) than with parallel group designs (as for metoprolol). Nevertheless, the decrease in pulse wave velocity with bisoprolol is compatible with the simple mechanical consequence of the blood pressure reduction itself.

The most important finding of the present study was the significant increase in arterial compliance observed in the brachial circulation. An increase in arterial compliance after β blockade has been noticed with β-blocking agents having ancillary properties such as pindolol or labetolol[3,17]; however, such compliance change has not been seen with noncardioselective β-blocking agents such as propranolol.[1,2] Whether such differences in vascular properties are directly related to the role of β_2 receptors in the vasculature of hypertensive patients remains an open question and requires further investigations.

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Cardiovascular Effects of Isradipine in Essential Hypertension

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The immediate and short-term cardiovascular effects of oral isradipine therapy were evaluated in 11 patients with mild to moderate systemic hypertension. Isradipine, 5 mg administered orally, induced a significant reduction in arterial pressure from 165 ± 6/88 ± 3 mm Hg to 140 ± 5/76 ± 2 mm Hg ($p < 0.001$) within 2.5 hours by a decrease in total peripheral resistance associated with an increase in heart rate and cardiac output. Contrary to the acute effect, oral therapy with isradipine for 3 months reduced arterial pressure through a decrease in total peripheral resistance but without causing an increase in heart rate or cardiac output or activation of the sympathetic nervous system. Isradipine slightly reduced left ventricular mass and improved cardiac systolic function and left ventricular filling. Renal blood flow increased, and renal vascular resistance ($p < 0.01$) and total blood volume ($p < 0.002$) decreased without a change in either sodium excretion or body weight. Thus, isradipine, when given for 3 months, decreased arterial pressure by reducing total peripheral resistance without activation of reflexive mechanisms. Its favorable effects on systemic hemodynamics, total blood volume, renal blood flow, and cardiac structure and function suggest isradipine to be an excellent choice for antihypertensive therapy.

(Am J Cardiol 1991;68:65–70)

Isradipine (PN 200-110) is a novel calcium antagonist of the dihydropyridine class with a chemical structure similar to that of nifedipine but with a benzofurazanyl group rather than a nitrophenyl group at position 4 of the pyridine. This substitution may impart specificity and selectivity of the drug with regard to the arterial tree. In animal studies, isradipine has been documented to be a very potent vasodilator with a long-lasting pharmacologic effect.[1–3] Unlike other available calcium channel blockers, it inhibits the sinus node with little effect on the atrioventricular node, and its negative inotropic effect is very weak.[4] Preliminary reports suggest that isradipine may benefit patients with congestive heart failure resulting from ischemic heart disease.[5–7] Because of these properties, isradipine appears to be a promising antihypertensive agent among the calcium antagonists; however, no clinical study has been published assessing the mechanism of its antihypertensive effect.[8–10] The present study was designed to evaluate the acute and short-term cardiovascular effects of isradipine in essential hypertension.

METHODS

Subjects: Eleven patients (8 men, 3 women, 9 white) with mild to moderate essential hypertension (World Health Organization Stage 1 to 2) were included in the study. Their ages ranged from 42 to 68 years (mean ± standard deviation 58 ± 2) with average body mass index (weight/height^2) of 30 kg/m^2 and average body surface area of 2.05 m^2. Patients with secondary forms of arterial hypertension were excluded. Most of the patients had never been treated or, for those who had been, all antihypertensive medication was discontinued ≥4 weeks before entry in the study. Two weeks before initiation of isradipine, patients received a placebo identical to the isradipine tablets. Patients were qualified for the study if, during treatment with the placebo, the diastolic blood pressure (phase 5 of Korotkoff) in the supine position was between 90 and 114 mm Hg on ≥2 consecutive outpatient visits before the baseline hemodynamic evaluation. However, after prolonged rest during the hemodynamic evaluation, values <90 mm Hg were recorded in some patients. Each subject provided informed consent to a protocol previously approved by the Institutional Clinical Investiga-

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TABLE I Acute Hemodynamic Effects of Isradipine (nine patients)

	2.5 Hours After		
	Pretreatment	First Dose	p Value
Systolic blood pressure (mm Hg)	166 ± 6	133 ± 3	<0.001
Diastolic blood pressure (mm Hg)	87 ± 3	72 ± 3	<0.001
Mean arterial pressure (mm Hg)	113 ± 4	92 ± 3	<0.001
Heart rate (beats/min)	68 ± 3	84 ± 4	<0.001
Left ventricular ejection rate (ml/s)	266 ± 27	334 ± 27	<0.001
Cardiac output (l/min)	5.58 ± 0.4	7.44 ± 0.55	<0.001
Stroke volume (ml/beat)	83 ± 6	89 ± 8	<0.05
Total peripheral resistance (U)	21 ± 1	13 ± 1	<0.001

tion Committee. After a baseline evaluation in the hemodynamic laboratory, 5 mg of isradipine was given orally to assess the acute response. After acute dosing, patients continued to take oral isradipine (2.5 mg twice daily). Blood pressure response was assessed every 2 weeks. If the therapeutic goal (diastolic pressure <90 mm Hg) was still not achieved, the dose was increased gradually to a maximal dose of 10 mg twice daily. Ten patients completed 12 weeks of treatment (short-term therapy).

Laboratory techniques: At the end of the placebo treatment, patients were studied in the hemodynamic laboratory after an overnight fast as previously described.[11] Briefly, an arterial catheter was placed in the aortosubclavian junction, and a venous catheter was placed in the superior vena cava by a modified Seldinger technique. Continuous recording of arterial pressure was obtained by a Statham P-23 pressure transducer, and simultaneous heart rate was monitored by electrocardiogram (lead II). Cardiac output was measured in triplicate with indocyanine green dye technique. Stroke volume, total peripheral resistance and left ventricular ejection rate were calculated by standard formulas. Resting supine hemodynamic measurements were performed before drug administration (baseline).

Measurements were repeated after upright tilt (48°) and a mental arithmetic test. Ten minutes of recovery were allotted between the maneuvers. In 9 patients, hemodynamics were reassessed 2.5 hours after oral administration of 5 mg of isradipine. In 10 patients who completed the study, the same hemodynamic evaluation was repeated after 12 weeks of isradipine therapy.

Plasma volume was measured during the hemodynamic study with ^{125}I-labeled serum albumin. Total blood volume was estimated from plasma volume and hematocrit (total blood volume = plasma volume/1− hematocrit). Central blood volume was assessed from the indocyanine green dye dilution curve by calculating the product of mean transit time and blood flow per second. Renal blood flow was determined by measuring the clearance of ^{131}I para-aminohippuric acid and splanchnic blood flow obtained from the plasma clearance of injected indocyanine green dye (50 mg). Glomerular filtration rate was determined by calculating creatinine clearance at 24 hours and by estimating plasma clearance of technetium-99m diethylenetriamine pentaacetic acid using 2 plasma samples.[12] Plasma renin activity, aldosterone and catecholamines were measured from arterial blood samples obtained after 1 hour of rest in the supine position both before and after short-term treatment. The samples were analyzed by radioimmunoassay and radioenzymatic assay, respectively.[13,14]

In 7 patients, a 2-dimensional guided, M-mode echocardiographic tracing of acceptable quality was obtained before and after short-term therapy by use of an ultrasonoscope (Toshiba SSA-60A) interfaced with a line scan recorder (LSR-20B) and a probe of either PSB-25A 2.5 MHz or PSB-37A 3.75 MHz. The technique for visualization of the left ventricle has previously been described.[15] Left ventricular posterior wall thickness, septal wall thickness, systolic and diastolic dimensions, and ejection time were measured using the Penn convention.[16] Each echocardiographic tracing was coded and read in a blinded manner by ≥2 investigators. Left ventricular mass was calculated according to the formula of Devereux and Reichek.[16] End-systolic wall stress was regarded as the most appropriate indicator for afterload.[17] Systolic left ventricular function was estimated by calculating the ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening, and ratio of end-systolic wall stress to end systolic volume index.[18] Diastolic function was determined with computer assistance as described by Upton and Gibson.[19] Septal and posterior wall endocardial echoes were digitized, and continuous plots were generated of left ventricular minor axis dimension versus time and the rate of change of dimension versus time. For each patient 3 to 5 consecutive cycles were analyzed and averaged. The peak filling rate of the left ventricle and the duration of rapid filling represent the diastolic func-

tion. An increase in peak filling rate or a decrease in duration of filling generally indicates improvement in left ventricular function.

Statistics: One-way analysis of variance with repeated measurements was used to compare baseline values with those after acute and short-term isradipine treatment. Linear correlation coefficients (Pearson) were calculated when indicated. Group data are expressed as mean ± standard error of the mean.

RESULTS

After 3 months of isradipine therapy, arterial pressure was well controlled in all patients. Only 1 patient (no. 6) withdrew because of blurred vision related to

TABLE II Short-Term Effects of Isradipine (10 Patients)

	Baseline	Short-Term	p Value
Systolic blood pressure (mm Hg)	165 ± 6	140 ± 5	<0.001
Diastolic blood pressure (mm Hg)	88 ± 3	76 ± 2	<0.001
Mean arterial pressure (mm Hg)	114 ± 4	97 ± 3	<0.001
Heart rate (beats/min)	69 ± 2	71 ± 3	NS
Left ventricular ejection rate (ml/s)	253 ± 21	267 ± 31	NS
Cardiac output (liters/min)	5.58 ± 0.40	5.94 ± 0.45	NS
Stroke volume (ml/beat)	83 ± 7	84 ± 6	NS
Total peripheral resistance (U)	21 ± 1	17 ± 1	<0.02
Norepinephrine (pg/ml)	209 ± 16	243 ± 22	NS
Epinephrine (pg/ml)	20 ± 3	26 ± 4	NS
Plasma renin activity (ng/ml/hour)	1.09 ± 0.18	1.54 ± 0.28	0.06
Aldosterone (ng/dl)	6.73 ± 1.15	7.88 ± 1.63	NS

NS = not significant.

TABLE III Left Ventricular Structure and Function at Baseline and After Short-Term Therapy with Isradipine

	Baseline Values	Short-Term Effect	p Value
Septal wall thickness (cm)	1.15 ± 0.03	1.06 ± 0.04	NS (=0.06)
Posterior wall thickness (cm)	1.08 ± 0.04	1.05 ± 0.03	NS
Diastolic dimension (cm)	4.79 ± 0.06	4.70 ± 0.1	NS
Left ventricular mass (g)	250 ± 12	225 ± 18	<0.05
Ejection fraction (%)	60 ± 2	63 ± 3	NS
Fractional fiber shortening (%)	32 ± 1	34 ± 2	NS
Velocity of circumferential fiber shortening (cir/s)	1.03 ± 0.07	1.21 ± 0.10	<0.05
ESWS (10^3dynes/cm^2)	60 ± 6	49 ± 6	<0.05
Contractility index (ESWS/ESVI) (10^3 dynes × m^2/ml × cm^2)	2.57 ± 0.13	2.60 ± 0.15	NS
Peak filling rate (cm/s)	7.23 ± 0.35	7.93 ± 0.43	NS
Duration of rapid filling rate (ms)	305 ± 18	269 ± 11	<0.05

ESWS/ESVI = end-systolic wall stress/end-systolic volume index; NS = not significant.

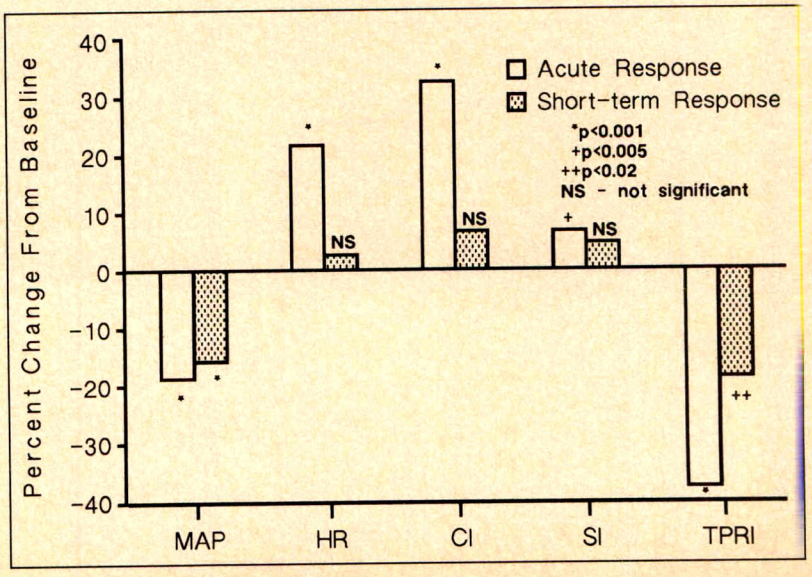


FIGURE 1. Acute and short-term hemodynamic response to isradipine. CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; NS = not significant; SI = stroke index; TPRI = total peripheral resistance index.

TABLE IV Effect of Isradipine on Fluid Volume State

	Baseline Value	After Short-Term Treatment	p Value
Body weight (kg)	91 ± 4	90 ± 5	NS
Total blood volume (ml)	6,071 ± 513	5,658 ± 472	<0.002
Plasma volume (ml)	3,704 ± 288	3,425 ± 278	<0.01
Central blood volume (ml)	2,572 ± 202	2,556 ± 183	NS
Ratio of central blood volume/total blood volume (%)	43 ± 1.5	46 ± 2.2	NS

NS = not significant.

the drug. One patient developed a symptomatic hypotensive response after the first dose but continued treatment thereafter. No other important adverse effects were observed.

Effect of acute administration: After the first oral dose of isradipine, a marked decrease in arterial pressure was observed (Table I). The decrease in arterial pressure was related to a significant reduction in total peripheral resistance, whereas heart rate and cardiac output increased (Table I). The increase in cardiac output was predominantly produced by an increase in heart rate and left ventricular ejection rate (Table I).

Short-term effect: After 3 months of isradipine treatment, the decrease in arterial pressure was less pronounced than it was after acute administration of the drug (Figure 1). Like the acute response, the decrease in arterial pressure was mediated mainly through a decrease in total peripheral resistance (Figure 1). Contrary to the acute response, however, heart rate and cardiac output returned almost to pretreatment levels after 3 months (Figure 1, Table II). Isradipine also produced a slight but significant decrease in left ventricular mass, from 250 ± 12 g before to 225 ± 18 g ($p < 0.05$) after treatment (Table III). Four patients showed a >10% decrease in left ventricular mass. End-systolic wall stress decreased from 60 ±6 10^3 dynes/cm^2 to 49 ± 6 10^3 dynes/cm^2 ($p < 0.05$), the velocity of circumferential fiber shortening increased from 1.03 ± 0.07 circ/s to 1.21 ± 0.1 circ/s ($p < 0.05$), and the duration of rapid filling improved from 305 ± 18 ms to 269 ± 11 ms ($p < 0.05$) (Table III). Plasma catecholamines and aldosterone did not change; however, the increase in plasma renin activity reached almost

TABLE V Effects of Isradipine on Regional Hemodynamics

	Baseline	After Short-Term Treatment	p Value
Renal blood flow (ml/min)	779 ± 59	936 ± 73	<0.01
Renal vascular resistance (U)	15.2 ± 0.98	11.2 ± 1.20	<0.01
Glomerular filtration rate (ml/min)			
Isotopic evaluation	127 ± 12	135 ± 11	NS
Creatinine clearance	118 ± 13	134 ± 8	NS
Filtration fraction (%)	15.4 ± 1.55	15.2 ± 1.42	NS
Splanchic blood flow (ml/min)	702 ± 39	638 ± 78	NS
Splanchic vascular resistance (U)	16.8 ± 0.95	17.9 ± 1.7	NS

NS = not significant.

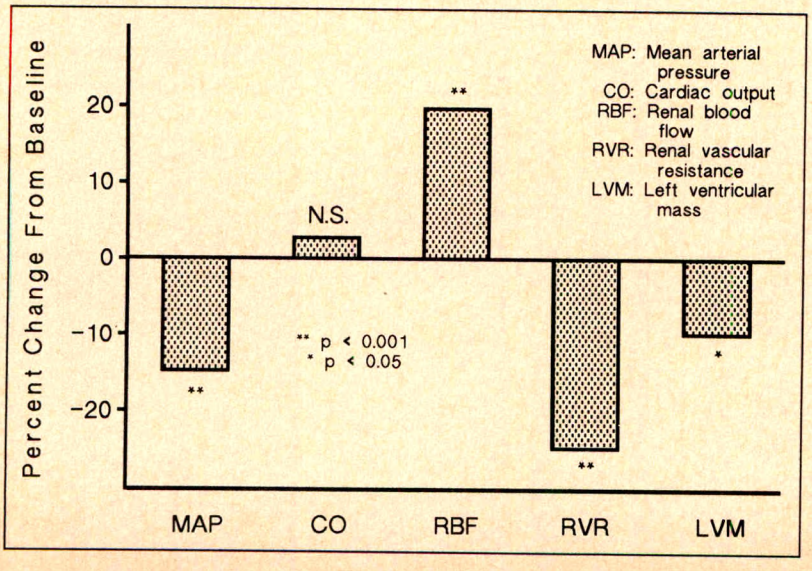


FIGURE 2. Effects of isradipine on target organs. N.S. = not significant.

TABLE VI Response to Stress Before and After Isradipine Therapy (percent change from control)

	Mental Stress (%)		Head-Up Tilt (%)	
	Before Therapy	After Therapy	Before Therapy	After Therapy
SBP	9.6 ± 3	9.5 ± 2	0.79 ± 1.2	−12.5 ± 5*
DBP	11 ± 3	10.7 ± 2	3 ± 2	−3.6 ± 5.9
MAP	10.2 ± 3	10 ± 2	2.1 ± 2	−8 ± 5*
HR	17 ± 5	11 ± 2	12.1 ± 2.7	15 ± 4.8
CO	17 ± 5	9 ± 4	7.9 ± 2.9	−15.9 ± 2.7
SV	0.25 ± 0.61	−1.31 ± 4.2	−18 ± 3	−26 ± 2
TPR	−4.7 ± 3	1.85 ± 3	−11.7 ± 3.3	−8 ± 4

*$p < 0.05$ versus before therapy.
CO = cardiac output; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; SV = stroke volume; TPR = total peripheral resistance.

significant levels (1.09 ± 0.18 vs 1.54 ± 0.28 mg/ml/hour; $p = 0.06$) (Table II). Total blood volume decreased ($p < 0.002$) without alteration in body weight and the ratio between cardiopulmonary and peripheral volumes (Table IV). Isradipine improved renal blood flow by reducing renal vascular resistance (Figure 2) and did not affect splanchnic blood flow or glomerular filtration rate (Table V). In 3 patients with a baseline glomerular filtration rate <120 ml/min, a remarkable increase occurred. Passive head-up tilt resulted in a greater decrease in arterial pressure after isradipine therapy (−8 ± 5% before vs 2.1 ± 2% after; $p < 0.05$) (Table VI). In 2 patients, a decrease in mean arterial pressure of 23 and 35%, respectively, was observed.

DISCUSSION

Acute and short-term isradipine treatment reduced arterial pressure by a decrease in total peripheral resistance. As with other calcium antagonists,[20,21] the acute effect was associated with a marked increase in cardiac output due to acceleration of heart rate. In contrast, in patients with congestive heart failure, Greenberg et al[5] observed no increase in heart rate after acute administration of isradipine. The absence of tachycardia in congestive heart failure may have been due to the fact that sympathetic response is often exhausted in these patients and not amenable to further stimulation.[22] Because the negative chronotropic effect of the drug is very weak,[4] the low dose of isradipine suffices to cause significant vasodilation but fails to inhibit the sinus node. Thus, the observed transient tachycardia was most likely the result of reflexive sympathetic stimulation.

Similar to the acute effect, arterial pressure was reduced by a decrease in total peripheral resistance after 3 months of oral isradipine therapy. However, this decrease was not associated with an increase in heart rate and cardiac output, and no evidence of sympathetic stimulation as reflected by plasma catecholamines levels was observed. In vitro studies documented that unlike verapamil and diltiazem,[23] isradipine exerted a minimal negative inotropic effect.[3] Our results of a somewhat improved systolic function support this observation in vitro. Similarly, indexes of diastolic function improved slightly, corroborating reports of other calcium antagonists.[24] Several calcium antagonists have been shown to reduce left ventricular mass in hypertensive patients.[20,21,25] In the current study, we also observed a slight regression of left ventricular mass, and in 4 patients a substantial decline of left ventricular mass was achieved. However, because our cohort is small, further studies are needed to confirm our results in this respect.

Unlike vasodilators, calcium antagonists do not produce sodium and water retention.[20,21] Unexpectedly, we found a significant decrease in total blood volume in the present study after 3 months of treatment. The natriuretic effect of isradipine has been described in animals and in a few clinical studies.[1,26] However, because our patients did not lose weight, the possibility of a capillary leak and volume redistribution to the extravascular compartment cannot be excluded.

Renal blood flow increased substantially because of a decrease in renal vascular resistance. Contrary to its effect on the renal vasculature, isradipine did not change splanchnic vascular resistance and splanchnic blood flow. Our observation confirms previous experimental studies showing that isradipine elicits vasodilation on the coronary, renal and cerebral arteries.[27] No consistent effect on the glomerular filtration rate was observed.

In patients with congestive heart failure, Greenberg et al[5] found no change in right atrial pressure after isradipine therapy. This might indicate that isradipine, like other calcium antagonists,[28] primarily dilates the arterial tree. However, in the current study, a mild but asymptomatic decrease in arterial pressure during passive head-up tilt test occurred, which might be related

to the volume contraction or to a subtle venodilation that becomes manifest only during passive tilt.

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Difference in Mortality Between Patients Treated with Captopril or Enalapril in the Xamoterol in Severe Heart Failure Study

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The double-blind, placebo-controlled, multinational trial Xamoterol in Severe Heart Failure randomized 290 patients treated with captopril and 217 treated with enalapril to xamoterol or placebo. At the end of the 100-day follow-up period, the cumulative probability of survival in patients with coronary artery disease or with dilated cardiomyopathy decreased in the captopril group (90.3%) when compared with the enalapril group (97.2%). The excess mortality in the captopril group could not be related to the indexes of the severity of heart failure, such as baseline exercise duration, functional class, cardiothoracic ratio, ejection fraction or dose of diuretic drugs. Furthermore, the excess in mortality was seen in all subsets of patients examined as well as across countries. Examination of the dosing regimen used, however, suggests that insufficient daily dosage of captopril or the inadequate schedule of administration, or both, might be responsible for different degrees of angiotensin-converting enzyme inhibition between the enalapril and captopril groups and hence for the difference in mortality. It is important in future clinical trials to determine to what extent complete circadian angiotensin-converting enzyme inhibition is necessary to provide the full benefit of this therapy in heart failure.

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The use of angiotensin-converting enzyme inhibitors in heart failure is supported by a large body of evidence showing improved exercise tolerance and quality of life in patients receiving these agents. Furthermore, in a controlled clinical trial, enalapril has been shown to reduce short-term mortality in patients with New York Heart Association functional class IV congestive heart failure.[1] Several other large trials currently examine the effects of these agents in heart failure but none has been undertaken to compare the effects of different angiotensin-converting enzyme inhibitors on mortality. In this respect, an intriguing observation came to the attention of the Steering Committee of the Xamoterol in Severe Heart Failure Study.[2] In this study, most patients were treated with either captopril or enalapril, and a discriminant analysis identified captopril treatment as one of the predictors of cardiac mortality.[2] Because of the widespread use of these drugs, the Steering Committee considered it important to examine in more detail the effect of captopril in this study.

METHODS

Patients: The study was a double-blind, randomized, between-group comparison of xamoterol (200 mg twice daily) and placebo, conducted at 66 centers in 10 countries (a listing of participating centers given in Reference 2). The study protocol has been reported in detail.[2] Briefly, patients were men or women with moderate to severe heart failure (New York Heart Association class III to IV) despite stable therapy with diuretic drugs and an angiotensin-converting enzyme inhibitor. The presence of left ventricular dysfunction had to be confirmed by 1 of the following criteria: cardiothoracic ratio >0.55, fractional shortening <20% (M-mode echocardiogram) or radionuclide ejection fraction <35%. Patients who had a myocardial infarction within 8 weeks, a significant aortic or pulmonary valve stenosis, hypertrophic cardiomyopathy, or patients capable of <1 minute of exercise on testing were excluded. After a placebo run-in period, patients were randomized to the double-blind treatment for 13 weeks with the xamoterol 2:1 placebo ratio. The study protocol was ap-

proved by ethical committees at each center and all patients gave their written informed consent. The mode of death in patients who died was determined on the basis of their records and on interview with the investigator concerned (given as progression of heart failure, sudden death or other cause). All deaths were included if they occurred within the study period of 91 days and during a further 9 days, covering 100 days of follow-up.

Difference in mortality between groups was analyzed on an intention-to-treat basis with use of life-table methods. The Kaplan-Meier survival curves were calculated using the SAS statistical package, and differences between the curves were analyzed with both the log-rank statistic and the Wilcoxon statistic. Comparison of the indexes of the severity of heart failure between groups were made using an unpaired t test or a

TABLE I Individual Clinical Data in the Enalapril Group

No. of Days	Age (yr) & Sex	Treat. Arm	Cause of Death	Etiology	NYHA	HR (beats/min)	Blood Pressure		CTR	Exercise Duration (sec)	Therapy*
							Systolic (mm Hg)	Diastolic (mm Hg)			
7	68M	X†	HF	CAD	4	80	110	70	0.62	110	30, DIU, DX
73	48M	X	HF	CAD	3	92	75	55	0.66	320	10, DIU, N
46	68M	X†	HF	CAD	4	56	140	100	0.47	360	40, DIU, DX
38	60M	X†	HF	CAD	4	120	120	80	0.60	140	20, DIU, N, DX
2	69M	X	HF	CAD	4	60	120	75	0.60	360	20, DIU, N, AA, CB
93	83M	X†	HF	CAD	3	84	102	60	0.58	250	10, DIU, N, DX
23	56M	X	Sud. D	CAD	3	96	120	90	0.51	605	5, DIU, AA, CB
40	65	Mean			3.6	84	112	76	0.58	306	Mean
34	11	±SD			0.5	22	20	16	0.07	166	±SD

*The numbers in this column are the daily dose of enalapril in milligrams.
†Patients withdrawn from their study drug at the time of death.
AA = antiarrhythmic; CAD = coronary artery disease; CB = calcium blockers; CTR = cardiothoracic ratio; CVA = cerebrovascular accident; DIU = diuretics; DX = digoxin; HF = death from progressive heart failure; HR = baseline resting heart rate; N = nitrates; NYHA = New York Heart Association; Sud. D = sudden death; SD = standard deviation; Treat. Arm = treatment arm; X = patients randomized to xamoterol.

TABLE II Individual Clinical Data in the Captopril Group

No. of Days	Age (yr.) & Sex	Treat. Arm	Cause of Death	Etiology	NYHA	HR (beats/min)	Blood Pressure		CTR	Exercise Duration (sec)	Therapy*
							Systolic (mm Hg)	Diastolic (mm Hg)			
39	61M	X†	Sud. D	DC	3	80	120	80	0.62	290	25, DIU, N, CB
7	44M	P	Sud. D	DC	4	75	100	75	0.55	420	50, DIU, AA
76	79M	X	Sud. D	DC	3	62	110	65	0.60	240	50, DIU, DX, N, CB
80	51M	X†	Sud. D	DC	3	60	120	80	0.55	550	37.5, DIU, DX
16	62F	X†	Sud. D	DC	3	100	160	80	0.78	164	75, DIU
88	45M	X	Sud. D	DC	4	84	110	80	0.57	490	50, DIU, DX, AA
35	70M	X	Sud. D	CAD	3	68	135	80	0.60	350	37.5, DIU, N, DX
76	67M	X†	Sud. D	CAD	3	88	160	100	0.61	300	25, DIU, DX
8	65M	X	Sud. D	CAD	3	80	130	95	0.53	680	25, DIU, N, CB
6	59M	X	Sud. D	CAD	4	72	140	90	0.56	310	12.5, DIU, N, CB
20	58M	X†	Sud. D	CAD	3	116	98	70	0.52	330	25, DIU, AA
33	63M	P	Sud. D	CAD	3	88	102	78	0.55	755	75, DIU, DX
40	69M	X	Sud. D	CAD	3	96	150	90	0.70	360	37.5, DIU, N, DX
66	73M	P†	HF	DC	4	72	130	80	0.65	300	75, DIU, N
35	68M	X†	HF	DC	3	72	180	110	0.63	240	75, DIU, DX
36	74F	X	HF	DC	4	76	130	80	0.60	180	37.5, DIU, N
66	54M	X†	HF	DC	4	72	78	60	0.64	106	50, DIU, N, DX, AA
67	50M	X	HF	DC	3	88	130	90	0.60	240	75, DIU, DX
82	68M	X	HF	CAD	4	76	115	75	0.56	150	75, DIU, N, DX
13	77M	P†	HF	CAD	3	76	175	80	0.60	570	12.5, DIU, DX
60	69M	X†	HF	CAD	3	85	110	70	0.58	400	200, DIU, CB
41	66M	X†	HF	CAD	3	95	100	60	0.58	350	75, DIU, N
10	66M	X†	HF	CAD	4	100	130	100	0.61	160	12.5, DIU, DX, AA
63	61M	X†	HF	CAD	4	76	100	80	0.57	255	25, DIU, N
68	69M	X†	HF	CAD	3	92	90	60	0.56	130	75, DIU
76	69F	X†	CVA	DC	3	75	170	90	0.69	80	18.5, DIU, AA
26	73M	P	CVA	CAD	3	80	120	80	0.65	270	37.5, DIU, DX
76	62F	X†	CVA	CAD	3	70	220	120	0.57	150	150, DIU, DX
47	64	Mean			3.3	81	129	82	0.60	315	Mean
27	9	±SD			0.5	13	32	14	0.06	170	±SD

*Numbers in this column are the daily dose of captopril in milligrams.
†Patients withdrawn from their study drug at the time of death.
P = patients randomized to placebo; other abbreviations as in Table I.

Mann-Whitney U test for normally and abnormally distributed variables, respectively.

RESULTS

A total of 516 patients had been randomized in the study, 352 to xamoterol and 164 to placebo, when the safety committee requested that the study be discontinued because of an excess of deaths in patients taking xamoterol.[2] Of these 516 patients, 290 were receiving captopril (85 in the placebo group, mean daily dose 61 mg, range 12.5 to 200 mg; 205 in the xamoterol group, mean daily dose 57 mg, range 6.25 to 200 mg), and 217 were receiving enalapril (75 in the placebo group, mean daily dose 10 mg, range 2.5 to 40 mg; 142 in the xamoterol group, mean daily dose 12 mg, range 2.5 to 40 mg). Nine patients received lisinopril and no death occurred in this small subgroup.

At the end of the 100-day follow-up period, 29 patients had died in the captopril group versus 9 in the enalapril group. The cumulative probability of death increased in the captopril group as a whole, with a 100-day probability of survival of 90.0 vs 96.3% in the enalapril group (2-tailed p values: log rank <0.0278, Wilcoxon <0.0286). Of the patients who died, 1 patient in the captopril group and 2 in the enalapril group had hypertensive heart disease. Tables I and II summarize the main clinical characteristics of the deceased patients with ischemic heart disease or idiopathic dilated cardio-

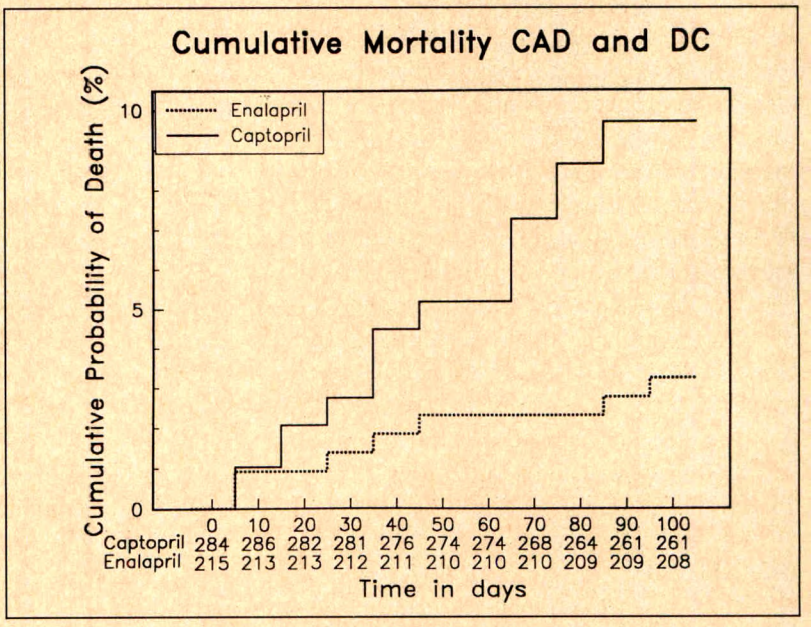


FIGURE 1. Cumulative probability of death in patients with heart failure resulting from coronary artery disease (CAD) or idiopathic dilated cardiomyopathy (DC) treated with enalapril or captopril during the 100-day follow-up.

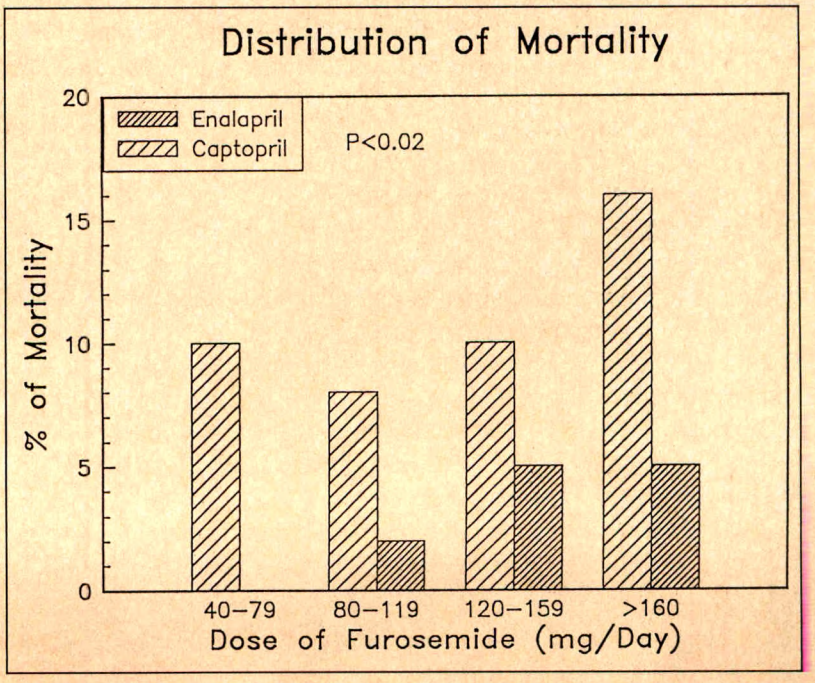


FIGURE 2. Distribution of mortality rate according to the dose of furosemide taken by the patients (only patients taking furosemide as their sole diuretic therapy were included). Comparison between distributions was made using a Kolmogorov-Smirnov test.

myopathy. In this subset, the difference in 100-day probability of survival between captopril and enalapril was large (90.3 vs 97.2%; 2-tailed p values: <0.016 log rank; <0.018 Wilcoxon) (Figure 1). The mean and median doses of captopril in the deceased patients were 54 and 50 mg, respectively, and 19 of 29 had received a dose of <50 mg/day. Furthermore, 16 of 29 patients received captopril twice daily. The mean and median doses of enalapril were 16.7 and 10.0 mg, respectively, administered on a once- or twice-daily basis.

There were no significant differences between groups with respect to age, functional class, baseline heart rate, systolic and diastolic blood pressures, cardiothoracic ratio or exercise duration. Similarly, these variables were comparable between the 2 groups of survivors. Concomitant therapies were also well matched between the 2 groups, and the excess mortality in the captopril group was still evident when the subgroup of patients receiving furosemide was stratified according to the dose given (Figure 2). The trend for an excess of mortality in the captopril group was also present when the subsets of patients with progressive heart failure (4.5 vs 2.8%) or sudden death (4.5 vs 1.4%) were considered. The excess in mortality with captopril was also noted in the placebo group (5.1 vs 1.4%). Finally, the effect appeared not to be center-dependent (United Kingdom — 8.8% deaths in the captopril group vs 2% in the enalapril group; Austria, Germany, Holland — 9.2 vs 4.9%; Belgium, Luxemburg, France — 11 vs 7.1%; Norway, Sweden — 11 vs 0%; South Africa — 13 vs 10%).

DISCUSSION

The excess in mortality evident in the captopril group must be examined with caution. The primary end point of the trial was not mortality and the patients were not randomly allocated to enalapril or captopril. In this respect, the statistical comparison of the survival curves may be criticized, but whether or not a "p" value is quoted, the differences in mortality appeared consistent enough to be of practical importance. Clearly, the data do not allow one to conclude that captopril was detrimental. The easiest hypothesis to explain the difference between groups was that patients with more severe heart failure had received captopril. Although this was not confirmed by the data available, it cannot be ruled out that despite comparable clinical signs of heart failure in the 2 groups, heart failure might have been present for a longer period of time in patients taking captopril, thus worsening their prognosis.

Captopril, on the other hand, has a shorter duration of action than enalapril[3] or lisinopril. It is less potent than enalapril on a milligram per milligram basis and it does not completely inhibit the converting enzyme. Its bioavailability is also reduced by food intake. Sixty-six percent of patients who died in the captopril group had received a dose lower than the recommended daily dose of 75 mg, and in many cases captopril was administered twice a day instead of the recommended 3 times a day. It is therefore possible that an incomplete inhibition of the converting enzyme in the captopril group, perhaps because of insufficient daily dosage, inadequate schedule of administration or poor compliance, reduced the protection provided by captopril. This hypothesis is supported by the fact that in a large trial assessing the effects of milrinone or placebo on mortality, a higher average dose of captopril was administered (75 mg), and in this trial the mortality in the enalapril and captopril groups appeared similar (Packer, personal communication).

Finally, because two-thirds of the patients also had received xamoterol, a detrimental interaction between this β_1 partial agonist and captopril is a possibility, although the trend was still present in the placebo group or after xamoterol withdrawal (Table II). The detrimental effects of xamoterol in the study may have been caused by the acute β blockade imposed by the drug in a setting of severe heart failure and high sympathetic drive, or by a β-stimulant effect when the sympathetic tone was low. Because captopril produces large circadian variations in the plasma levels of angiotensin II—a major modulator of the sympathetic drive—larger swings in sympathetic drive might have been present in the captopril than in the enalapril group. This might have caused greater variations between the agonist and antagonist activity of xamoterol in the captopril group.

In conclusion, these results suggest the importance of assessing to what extent complete circadian angiotensin-converting enzyme inhibition is necessary to provide the full benefit of this therapy in heart failure.

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Determinants of One-Year Outcome from Balloon Aortic Valvuloplasty

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Balloon aortic valvuloplasty (BAV) has been a therapeutic alternative treatment for severe symptomatic aortic stenosis. Previous studies have been unable to predict 1-year outcome because of limited acute and follow-up clinical, invasive and echocardiographic data. The purpose of this study was to predict long-term outcome based on comprehensive data obtained at the time of valvuloplasty and at 3 and 6 months after the procedure. Of 170 consecutive patients undergoing BAV, 108 (mean age 78 years) were at least 1 year from their procedure. Prospective clinical, micromanometer hemodynamic, digital ventriculographic and echocardiographic/Doppler data were collected at baseline and immediately after the procedure. Echocardiographic data were also obtained at 3 and 6 months. With use of Cox model analysis, major events (defined as cardiac death [n = 30], aortic valve replacement [n = 21] or repeat BAV [n = 13]) were predicted by advanced age, baseline heart failure class, and baseline echocardiographic-determined diastolic left ventricular diameter. Only baseline left ventricular ejection fraction proved to be a significant predictor of cardiac death (p = 0.002) in a multivariate model. Absolute values after BAV (stroke work, first derivative of left ventricular pressure, valve area, end-systolic volume, Fick cardiac output, transvalvular gradient) and acute changes measured by catheterization or echocardiography did not provide additional predictive information over that of postprocedure ejection fraction. Similarly, echocardiographic valve area and transvalvular gradient at 3 months added no further prognostic data. With an ejection fraction ≥45% (n = 63), cardiac survival at 1 year was 80%, irrespective of age, sex, congestive heart failure class or severity of coronary artery disease.

Thus, prognosis after BAV can be determined by noninvasive clinical and echocardiographic data obtained before cardiac catheterization. Despite advanced age and concomitant medical problems, patients undergoing BAV with baseline ejection fractions ≥45% have an excellent cardiac survival to 1 year.

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Balloon aortic valvuloplasty (BAV) has been an alternative treatment for severe aortic stenosis.[1–6] Although restenosis and recurrent symptoms occur often at a variable time after the procedure, some patients experience sustained improvement.[1–12] Previous studies have described short-term predictors of outcome, based on either invasive or noninvasive parameters.[3–7] However, analysis of factors predictive of long-term outcome have yet to be delineated. In an elderly and debilitated population of patients, BAV often represents the only treatment option other than medical therapy. Therefore, it becomes important to clarify its role in the treatment of symptomatic aortic stenosis.

Controversy exists as to what factors, if any, constitute a successful procedure (e.g., final aortic valve area, and changes in aortic or echocardiographic valve areas 1 to 3 days after BAV).[3–7] Previous studies have limited long-term data and have typically failed to analyze both invasive, hemodynamic and serial echocardiographic data and their relation to patient outcome. Prospective determination of clinical, hemodynamic or echocardiographic variables predictive of 1-year outcome would help clarify the patient groups that are likely to benefit from BAV. This study identifies the clinical, acute hemodynamic and echocardiographic variables that predict 1-year outcome after BAV, and determines whether 3- or 6-month echocardiographic data provide additional prognostic information.

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METHODS

Patient population: Of 170 consecutive patients undergoing BAV at Duke University Medical Center, 108 had undergone valvuloplasty at least 1 year previously and thus were eligible for 1 year follow-up. BAV was performed in patients that were deemed high risk for aortic valve replacement after all patients were evaluated by cardiology and cardiothoracic surgery. The median age was 78 years (range 53 to 91). Forty-four percent were men. Before BAV, all patients had severe symptomatic aortic stenosis and were in either New York Heart Association Functional class III or IV congestive heart failure (n = 86) or Canadian Functional class III or IV angina (n = 49), or both. Based on digital subtraction supravalvular aortography and 2-dimensional echocardiography, the cause of aortic stenosis was assumed to be senile degenerative calcific aortic stenosis in 96 and bicuspid aortic stenosis in 12. Significant coronary artery disease was present in 59 (55%). Fourteen had significant 3-vessel disease. Significant disease was usually defined as ≥75% luminal diameter narrowing.

Valvuloplasty procedure: BAV was performed after informed consent from a previously approved institutional review board protocol. A 20-mm balloon was used as the initial balloon in all patients. The retrograde technique using a single balloon (Mansfield, Inc., Mansfield, Massachusetts) of 20 or 23 mm was used in 92 and 6 patients, respectively. Double balloons of 20 and 10 mm were used in 10 patients.

Left ventricular and aortic pressures were simultaneously measured immediately before and after BAV with dual-sensor, high-fidelity micromanometer catheters (Millar, Inc., Houston, Texas). R-wave gated masked-mode digital subtraction left ventriculography and supravalvular aortography were obtained before and after the intervention in 106 of 108 patients. Left ventricular volume was calculated with the area-length formula and a regression equation based on 20 previously calibrated human heart casts of known volume. Aortic regurgitation was graded 0 to 4+ with a standard angiographic grading scale.

Angiographic images were acquired with an ADAC 4100-C digital radiography system interfaced with a GE- MPX L/U x-ray unit. Images were recorded in a 9-inch image intensifier mode using a 256 × 256 × 8 pixel matrix at 30 frames per second.

Oxygen consumption was measured with a metabolic cart and Fick cardiac output was obtained. The effective aortic valve area was calculated using the Gorlin formula.

Echocardiographic data: Echocardiographic data were obtained with a Hewlett-Packard 77020A phased-array sector scanner immediately before and 1 to 3 days after valvuloplasty in all patients. Fifty-eight patients underwent a 3-month echocardiographic study, and 53 patients a 6-month study. Left ventricular end-diastolic dimension was measured from the parasternal view using M-mode or 2-dimensional imaging according to the recommendations of the American Society of Echocardiography.[13,14] Subaortic diameter was measured immediately below the aortic cusps in the long-axis parasternal view. The subaortic area was calculated from diameter measurements during 3 to 5 beats in systole. Subaortic velocity was measured by pulsed Doppler and displayed by fast-Fourier transform spectral analysis. Signals were obtained from the cardiac apex with a cursor positioned in the outflow tract at the same level as the diameter measurement. Transducer angulation was optimized to obtain maximal velocity. Peak systolic velocity was calculated for 5 cardiac cycles in patients with sinus rhythm and 10 cycles in patients with atrial fibrillation.

Continuous-wave Doppler was performed with a 1.9-MHz transducer, and velocities were optimized. Peak instantaneous and mean gradients were calculated from resident software. Aortic valve area was calculated with the continuity equation.[15]

Patient evaluation: Patient status was evaluated by physician interview and examination at baseline and at 3 months, 6 months and 1 year after BAV. End points were achieved when the patient died, underwent aortic valve replacement, underwent repeat BAV, or survived to 1 year after the procedure. If death occurred, telephone interview with both the primary care physician and family were obtained in order to classify the cause as either cardiac or noncardiac.

Statistics: All continuous results were expressed as median (twenty-fifth, seventy-fifth percentile). Categorical variables were expressed as percentages. The Kaplan-Meier method[16] was used to calculate median survival rates. All patients were followed for 1 year unless they died or had a major event, at which date they were withdrawn and analyzed as alive (i.e., event-free).

To evaluate the changes in values from before to after valvuloplasty, paired *t* tests were used after the assumption of normality was checked and accepted. A Wilcoxon rank-sum test was used to compare baseline echocardiographic measurements in patients with and without a 3-month echocardiogram.

Because of the large number of variables collected in relation to the relatively small number of events, a subset of potential prognostic variables from each of the categories (clinical, hemodynamic 1, hemodynamic 2 and echocardiographic) was identified. The Cox proportional-hazards regression model[17,18] was used to ex-

amine the univariable relation of each with the outcomes of cardiovascular death and total cardiac events (cardiac death, aortic valve replacement or repeat valvuloplasty).

When the relation between the variable of interest and the logarithm of the hazard ratio was assumed to be linear, spline functions[19–21] were used to describe the true shape. These graphically displayed functions were then used to ascertain the appropriate transformations required to meet the linearity assumption.

Further variable reduction was required; thus, the stepwise technique was used within each of the 4 categories for each outcome. The resultant 4 sets of variables were then used in a final model, again using stepwise techniques to describe best the joint relation of these with each of the 2 outcomes.

The added prognostic value of 3- and 6-month echocardiograms was evaluated by adding them as time-dependent covariates into Cox proportional-hazards models, which included the baseline echocardiographic data and the baseline resultant variable(s) from stepwise regression as fixed covariates.

RESULTS

Patient outcome: The demographics of the study group are listed in Table I. The median time for follow-up was 252 days (range 105 to 471 days). All patients were potentially eligible for 1 year of clinical follow-up. There were 35 deaths, 30 of which were cardiovascular. Death occurred at a median of 125 days (48, 248 days). Specific causes of cardiovascular death were progressive congestive heart failure in 17, sudden death in 7, stroke in 2 and undetermined cardiovascular causes in 4. Other major events included 21 patients who underwent aortic valve replacement, and 13 requiring repeat BAV owing to recurrent symptoms and restenosis. The probability of event-free survival was 38% at 1 year and the probability of cardiac survival was 65% at 1 year (Figure 1).

Of the 73 patients who were alive at 1 year, 28 had overall improved symptoms, 11 had symptoms that returned to baseline, and 34 were considered to have overall worse symptoms than before BAV.

Congestive heart failure was present at baseline in 86 patients, and was improved by at least 1 functional class in 24 of 27 patients who had not incurred a major event at 1 year. Twenty-six cardiac deaths occurred, 17 had an aortic valve replacement, 12 underwent repeat BAV and 4 noncardiac deaths occurred.

Canadian functional class III or IV angina was present in 49 patients before BAV. Twelve of 13 patients evaluated at 1 year were improved by at least 1 functional class. Fifteen incurred a cardiac death, 12 required aortic valve replacement, 7 underwent repeat dilation and 2 noncardiac deaths occurred.

TABLE I Distribution of Baseline Clinical and Catheterization Characteristics

Characteristics	Number
Age (years)	78 (72, 82)
Men/women	48/60
Number of coronary arteries narrowed >50% in diameter	
1	28 (26%)
2	18 (17%)
3	14 (13%)
Ejection fraction (%)	52 (31, 61)
Ejection fraction <45%	44 (41%)
Congestive heart failure (class III or IV)	86 (80%)
Angina (class III or IV)	50 (46%)
Syncope	35 (32%)

Continuous variables reported as median (25th, 75th percentile). Other variables reported as percentages.

Hemodynamic results: BAV resulted in an acute significant decrease in left ventricular to aortic peak-to-peak and mean gradients, from 70 (50, 90 mm Hg) to 38 mm Hg (28, 50 mm Hg) ($p < 0.0001$) and 58 (40, 73 mm Hg) to 35 mm Hg (26, 45 mm Hg) ($p < 0.0001$), respectively. Mean aortic valve area increased from 0.50 (0.4, 0.6 cm^2) to 0.80 cm^2 (0.6, 0.9 cm^2) ($p < 0.0001$). Peak aortic systolic pressure declined from 147 (128, 167 mm Hg) to 141 mm Hg (123, 158 mm Hg) ($p = 0.005$). Left ventricular systolic and end-diastolic pressure decreased from 210 (183, 239 mm Hg) to 180 mm Hg (155, 200 mm Hg) ($p < 0.0001$) and 20 (15, 30 mm Hg) to 15 mm Hg (10, 23 mm Hg) ($p < 0.0001$), respectively. Left ventricular ejection fraction increased from 52 (31, 61%) to 55% (32, 63%) ($p = 0.0001$). An acute increase in ejection fraction of >5 units was noted in 28 of 105 patients. Left ventricular end-diastolic and end-systolic volumes both decreased from 125 (100, 166 ml) to 120 ml (94, 155 ml) ($p < 0.036$) and 58 (38, 94 ml) to 57 ml (36, 92 ml) ($p < 0.0002$), respectively. Stroke

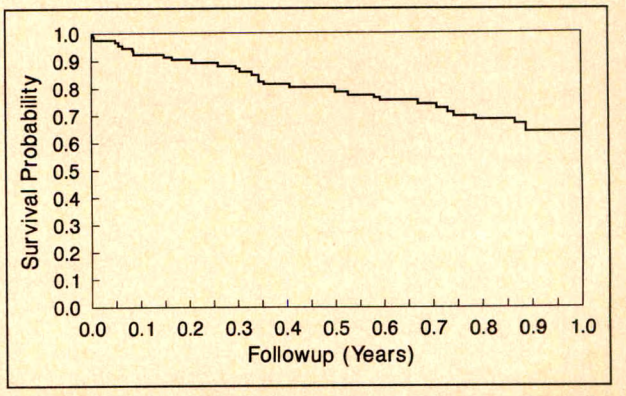


FIGURE 1. Probability of cardiac survival at 1 year after balloon aortic valvuloplasty.

TABLE II Baseline Variables: All Major Events

	Univariable Chi-Square Analysis	
	Cardiac Death	Total Events
Clinical		
Congestive heart failure	8.05	8.73
Women	3.59	6.19
Coronary artery disease	2.00	2.12
Age	1.33	10.26
Angina	1.14	4.90
Hemodynamic		
Ejection fraction	18.07	21.23
End-diastolic pressure	8.61	8.40
End-systolic volume	8.09	17.62
Cardiac output	7.61	5.07
Peak gradient	7.26	3.72
Max. (+) dP/dt	7.20	14.85
Max. (−) dP/dt	3.27	14.23
End-diastolic volume	2.48	10.07
Aortic valve area	1.44	0.52
Echocardiographic		
Peak gradient	18.21	15.80
Mean gradient	17.96	14.44
Left ventricular internal diameter-diastole	9.98	21.83
Left ventricular posterior wall thickness	1.27	1.35
Aortic valve area	1.03	3.01

Max. dP/dt = maximal rate of rise of left ventricular pressure (+ = positive; − = negative).

work decreased from 12 (9, 16 ergs × 10^6) to 11 ergs × 10^6 (7, 15 ergs × 10^6) ($p < 0.0001$), as did peak (+) first derivative of left ventricular pressure [dP/dt] (1,700 [1,300, 2,000 mm Hg/s] to 1,600 mm Hg/s [1,200, 1,900 mm Hg/s]) ($p < 0.0001$). Peak negative dP/dt increased from −1,725 (−1,500, −2,175 mm Hg/s) to −1,337 mm Hg/s (−1,575, −1,000 mm Hg/s) ($p < 0.0001$). Aortic regurgitation increased by 1 grade in 6 patients and decreased by 1 grade in 10 patients. One patient had a change of >1 grade in the severity of aortic regurgitation.

Echocardiographic results: The median peak instantaneous and mean transvalvular gradient were decreased at the 1- to 3-day echocardiographic study: 79 (61, 96 mm Hg) to 65 mm Hg (48, 79 mm Hg), ($p < 0.0001$) and 49 (36, 60 mm Hg) to 39 mm Hg (28, 50 mm Hg), ($p < 0.0001$), respectively. Median aortic valve area increased from 0.50 (0.30, 0.60 cm^2) to 0.60 cm^2 (0.40, 0.80 cm^2) ($p < 0.0001$).

Ninety-three patients were alive at 3 months, and a 3-month echocardiogram was obtained in 58 (62%) of these patients. When compared with patients who did not return for the 3-month study, both aortic valve area and mean gradient soon after BAV were similar; 0.60 (0.40, 0.80 cm^2) vs 0.60 cm^2 (0.40, 0.80 cm^2) ($p = 0.47$) and 40 vs 37 mm Hg ($p = 0.075$), respectively. At 3 months, the peak and mean gradients were higher, although insignificantly, than they were after the procedure: 65 (48 to 79 mm Hg) vs 67 mm Hg (53 to 84 mm Hg) ($p < 0.25$) and 39 (28, 50 mm Hg) vs 41 mm Hg (33, 52 mm Hg) ($p < 0.075$), respectively. The aortic valve area decreased from 0.60 (0.40, 0.80 cm^2) to 0.50 cm^2 (0.40, 0.70 cm^2) ($p < 0.006$).

Fifty-three (78%) of 68 patients who were alive at 6 months underwent an echocardiographic study. At 6 months, the peak and mean gradients had returned to baseline at 78 (61, 96 mm Hg) and 49 mm Hg (36, 62 mm Hg), respectively. Aortic valve area also returned to baseline, 0.5 cm^2 (0.4, 0.6 cm^2).

Predictors of patient outcome: The baseline clinical, hemodynamic and echocardiographic variables and their univariate association with any major event (cardiac death, aortic valve replacement or repeat BAV) or cardiac death alone are listed in Table II. In using the log of the hazards ratio, all variables except end-systolic volume met the assumption of linearity. Mortality is lowest in patients with low end-systolic volumes and increases until a volume of approximately 135 ml is reached. No additional gradient in mortality occurs beyond 135 ml.

For the prediction of major events, age and congestive heart failure jointly described the relation for the clinical variables. Once left ventricular ejection fraction is known, no other ventriculographic variable adds significant information. Similarly, for the hemodynamic and echocardiographic variables, end-systolic volume and left ventricular internal diameter during diastole, respectively, significantly describe all information contained in those categories.

The combination of these 5 variables resulted in a final model of left ventricular internal diameter, congestive heart failure, and age best predicting total events (chi-square = 33, degrees of freedom (df) = 3). The predictive ability of left ventricular ejection fraction with congestive heart failure and age is almost identical (chi-square = 32, df = 3).

Only 1 baseline variable from each category proved in multivariate analysis to be significant in predicting cardiac survival: clinical, congestive heart failure; he-

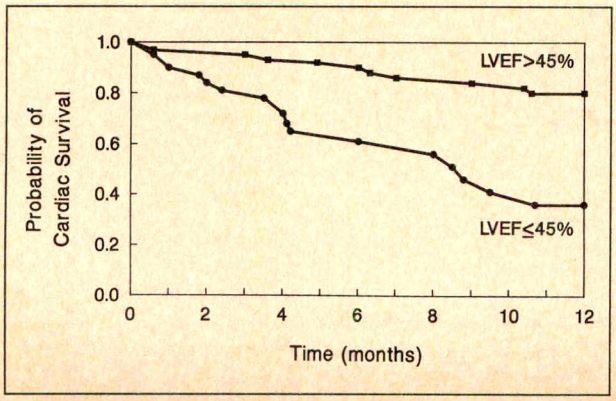


FIGURE 2. Probability of cardiovascular death based on baseline left ventricular ejection fraction (LVEF).

modynamic 1, left ventricular ejection fraction; hemodynamic 2, end-systolic volume; and echocardiography, peak instantaneous gradient. When combining all variables in the model, 78% of the information was explained by baseline left ventricular ejection fraction and 22% by peak gradient, together containing all of the significant information (chi-square = 23, df = 2). The probability of cardiac survival based on baseline ejection fraction is shown in Figure 2. With an ejection fraction ≥45%, cardiac survival at 1 year was 80%.

Multivariable analysis of variables alone after BAV indicated that ejection fraction alone after BAV was needed in predicting cardiac death. In particular, final aortic valve area by catheterization or echocardiography did not contain univariably significant information. Likewise, the absolute change in aortic valve area determined by catheterization or echocardiography or in ejection fraction did not significantly improve the prognostic ability over that of baseline ejection fraction alone.

Fifty-eight patients had a 3-month echocardiogram performed. Fifty-three of these also had a 6-month echocardiogram available. Fifteen patients died of cardiovascular causes by 3 months and an additional patient had died by 6 months. When models with baseline ejection fraction and echocardiographic information were compared with models containing the same plus the 3-month information, results show no significant additional prognostic information in the 3-month echocardiogram.

The addition of the 6-month echocardiogram to the model is also insignificant for prediction of 1-year survival once the baseline information is known (Figure 3).

DISCUSSION

Cardiovascular death at 1 year in patients undergoing BAV appears to be closely related to baseline left ventricular ejection fraction. This study, representing the largest series of patients with clinical, hemodynamic and echocardiographic data available, reveals that a baseline ejection fraction ≥45% portends an excellent 1-year cardiac survival. This is irrespective of advanced age, extent of coronary artery disease, heart failure class or sex.

When examining clinical, hemodynamic and echocardiographic factors predictive of any major event, it appears that noninvasive parameters, i.e., congestive heart failure class, age, and left ventricular internal diameter at end-diastole are independent predictors. Therefore, major events after BAV can be prospectively determined by noninvasive characteristics rather than diagnostic cardiac catheterization. This should be an important consideration in this often elderly population of patients. Noninvasive data should provide a means for answering the potential 1-year efficacy of BAV.

Symptomatic restenosis is a common occurrence after BAV and is particularly so in patients with depressed left ventricular function. One-year survival in patients with poor ventricular function is dismal (36%). However, in patients with preserved function, cardiovascular survival appears excellent after BAV. Controlled studies will be necessary to delineate whether BAV can impact on survival in patients with preserved left ventricular function. Previous studies examining the natural history of medically treated aortic stenosis may not be relevant to this patient population.[22,23]

An additional echocardiogram at 3 or 6 months did not appear to provide further prognostic insight than what was available before BAV. Six-month echocardiograms were recorded in 53 patients who were alive at that follow-up date. It is possible that the lack of added predictive value of the 6-month echocardiogram resulted from these data being available in a smaller subset of patients. However, this cohort represented 78% of patients alive at 6 months. Similarly, the acute changes noted at catheterization immediately after BAV or the echocardiogram at 1 to 3 days after BAV were not helpful.

Previous studies evaluating patient outcome after BAV have been limited by reporting only short-term (3- to 6-month) outcome, or have not examined clinical, hemodynamic and echocardiographic data in the same cohort of patients.[3–6] Thus, potential interactions and additional prognostic information available from a complete patient evaluation have not been previously elucidated. Other studies have concluded that baseline left ventricular function is a strong predictor of 3- and 6-month clinical outcome.[3,4,10] Although ejection fraction has been shown to increase acutely and at follow-up in a subset of patients undergoing BAV,[12,24] the acute change in ejection fraction does not assist in predicting 1-year outcome. Similar results have been ob-

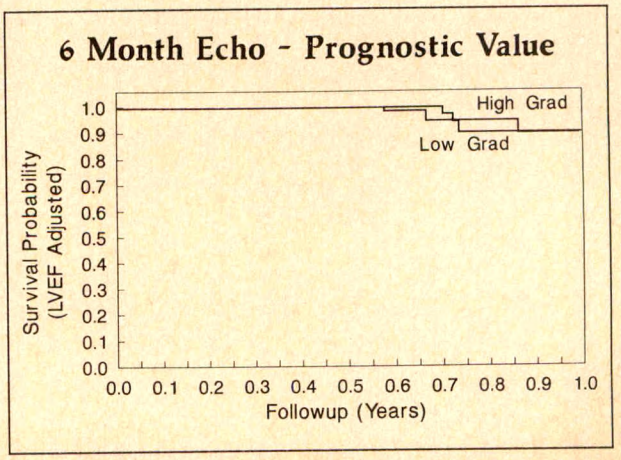


FIGURE 3. Cardiac survival in patients with high and low peak gradient (Grad) by echocardiography at 6 months after balloon aortic valvuloplasty adjusted for baseline ejection fraction (LVEF).

served for prospectively determining 3-month symptomatic status.[4]

This study reveals that the most extensive hemodynamic evaluation may not be necessary to stratify patients undergoing BAV. Rather, a baseline ejection fraction may be the most important piece of data that can be obtained to predict cardiovascular survival. This occurs despite the known afterload dependence of ejection phase indexes such as the ejection fraction. Any major event, i.e., death, aortic valve replacement or repeat BAV, can likewise be determined prospectively by noninvasive means. A clinical history or echocardiogram would provide all the information necessary to predict events within the first year after BAV.

Ejection fraction derived from digital subtraction ventriculography is highly correlated with radionuclide angiocardiography ($r = 0.95$, standard error of the estimate = 0.05).[25] Therefore, if noninvasive measures including clinical history, echocardiography or radionuclide angiography, or both, could be used to identify patients likely to have at least 1-year survival, then unnecessary invasive diagnostic and interventional procedures may be precluded in this often debilitated population. Thus, the present study demonstrates that cardiac survival can be expected at 1 year after BAV if baseline left ventricular function is preserved. Because the severity of coronary artery disease and other parameters of left ventricular or valvular function did not add to the predictive value of ejection fraction, radionuclide evaluation of ejection fraction should suffice to determine 1-year prognosis and help select patients likely to benefit from the procedure.

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Relation Between Myocardial Beta-Adrenergic Receptor and Left Ventricular Function in Patients With Left Ventricular Volume Overload Due to Chronic Mitral Regurgitation With or Without Aortic Regurgitation

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The relation between myocardial β-adrenergic receptor and left ventricular (LV) function was studied in 10 patients, aged 41 to 61 years (average 51), with LV volume overload mainly due to chronic mitral regurgitation. Beta-adrenergic receptors were examined using crude membrane in LV papillary muscle obtained at mitral valve replacement. Cardiac function was evaluated at preoperative cardiac catheterization with the interval to surgery of 1 to 33 months (average 7). Beta-adrenergic receptor density in 7 patients with New York Heart Association class II or III congestive heart failure was higher than that in 3 patients with class IV heart failure (59 ± 19 vs 37 ± 3 fmol/mg protein, $p < 0.05$). Beta-adrenergic receptor density showed a positive correlation with end-systolic stress/end-systolic volume index ratio, the index for contractile function ($p < 0.005$). Other parameters such as cardiac index, pulmonary artery wedge pressure and LV ejection fraction had no significant correlation to β-adrenergic receptor. The results demonstrated that increases in symptom and LV dysfunction, particularly of the contractile state, was associated with decreased myocardial β-adrenergic receptor density from possible down-regulation in patients with chronic mitral regurgitation with or without aortic regurgitation.

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Myocardial β-adrenergic receptor density has been described as decreased in patients with end-stage congestive heart failure due to cardiomyopathy or ischemic heart disease.[1–5] This has been recognized as the down-regulation of the β-adrenergic receptor system. In valvular heart disease, congestive heart failure is also a common finding at its end stage, particularly of mitral regurgitation (MR) or aortic regurgitation (AR) with left ventricular (LV) volume overload. However, the status of myocardial β-adrenergic receptor has been less elucidated in patients with advanced valvular disease.[6–8] In these volume-loaded hearts, the LV contractile state has been known to correlate with the progression of heart failure,[9] and the β-adrenergic receptor system may also be altered with the worsening of valvular disease. The aim of the present study was to clarify the relation between myocardial β-adrenergic receptors examined in mitral papillary muscle and LV function, as well as the degree of heart failure in patients with LV volume overload due to chronic MR with or without AR.

METHODS

Clinical and hemodynamic findings of patients: Ten patients were entered into this study, (6 with chronic MR had received mitral valve replacement and 4 with chronic MR combined with chronic AR had received mitral and aortic valve replacement). All patients had received digitalis glycosides and 3 had taken nitrates. No patient received catecholamines before operation. Cardiac catheterization was performed at an average interval to surgery of 7 months. End-systolic stress was calculated from Mirsky's formula.[10] The method of LV volumetry and other measurements at cardiac catheterization have previously been described in detail.[9] All clinical and hemodynamic data are summarized in Table I.

Myocardial samples: Under hypothermic cardiopulmonary bypass, aortic cross-clamp was performed followed by myocardial protection with a potassium car-

TABLE I Patient Characteristics

Pt.	Age (yr) & Sex	Lesion and Degree	NYHA Class	Interval (mos)	CI (liters/min/m^2)	PCWP (mm Hg)	LVEDVI (ml/m^2)	LVEF (%)	ESS/ESVI (Kdynes · m^2/cm^5)
1	41F	MR(III)	II	5	3.63	23	130	62	3.86
2	58F	MR(III)	III	14	3.50	25	90	54	4.26
3	61F	MR(III)	III	1	1.58	13	86	59	4.77
4	46M	MR(IV)	III	33	3.61	22	170	52	2.93
5	53F	MR(III)	II	8	2.06	26	87	56	6.71
6	52F	MR(IV)	III	1	2.09	20	114	61	4.41
7	47M	MR(III) + AR(III)	IV	1	2.00	8	345	51	1.16
8	53M	MR(III) + AR(IV)	IV	1	3.04	40	355	29	1.70
9	48M	MR(III) + AR(IV)	IV	2	1.80	8	291	36	1.49
10	53M	MR(III) + AR(III)	III	7	1.98	18	171	55	3.13
Mean ± SD	51 ± 6			7 ± 10	2.52 ± 0.77	21 ± 8	183 ± 101	51 ± 10	3.44 ± 1.63

AR = aortic regurgitation; CI = cardiac index; Degree = defined according to Sellers classification using angiographic method; ESS/ESVI = end-systolic stress/end-systolic volume index; Interval = from catheterization to surgery; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PCWP = pulmonary artery wedge pressure.

dioplegic solution and topical cooling. LV papillary muscles were obtained when excising the subvalvular apparatus of the mitral valve for mitral valve replacement. Average duration from the beginning of aortic cross-clamp and removal of the papillary muscle was 13 ± 3 minutes (range 9 to 19). Immediately after excision, specimens were placed in liquid nitrogen at −70°C.

Measurement of beta-adrenergic receptors: A crude myocardial membrane preparation was made from LV papillary muscles according to the method described by Fowler et al.[4] A previously frozen biopsy specimen was placed in 10 ml of ice-cold 10 mM Tris, 1 mM ethylene glycol-bis-(beta-amino-ethylether) N, N′-tetra-acetic acid buffer, pH 8.0, and grossly visible fibrous tissue was dissected free. The remaining sample was compiled as an aggregate, blotted dry and weighed. Tissue weight ranged from 128 to 207 mg (mean ± standard deviation 167 ± 10 mg). The samples were placed in 40 ml of ice-cold Tris buffer and homogenized in a polytron by 3 consecutive 3-second bursts at the maximal power setting of 11. One milliliter of ice-cold 2.5 M potassium chloride was then added to extract contractile proteins, followed by stirring at 4°C for 15 minutes. The suspension was then centrifuged at 50,000 g for 15 minutes and resuspended with a quick burst in the polytron and recentrifuged and resuspended in the same manner. After a third centrifugation the preparation was suspended in the final buffer for receptor-binding assay.

The radioligand (−)[^{125}I]iodocyanopindolol, which has been used for identifying β-adrenergic receptor, was used in this study. The assay buffer was 20 mM Tris-hydrogen chloride, 150 mM sodium chloride and 1 mM ascorbic acid, pH 7.5 at room temperature. Duplicate tubes containing 6 increasing concentrations of [^{125}I]iodocyanopindolol from 5.0×10^{-12} to 1.5×10^{-10} M with or without 10^{-6} M (−) propranolol for a total volume of 150 μl were prepared. The assay was begun with the addition of 300 μl of membrane preparation, and then incubated for 90 minutes at 37°C. This condition allowed for complete equilibration of the receptor with the radioligand. Bound and free ligands were separated by the addition of 5 ml Tris buffer (room temperature), rapid filtration through Whatman GF/F filters and immediate washing with an additional 15 ml of the same buffer. Filters were counted at 70% efficiency in a gamma counter (Packard, model Minaxi-r). Specific binding was defined as the difference in binding in the absence and the presence of 10 μM (−) propranolol. Beta-adrenergic receptor density and dissociation constants of binding sites were obtained in individual experiments from Scatchard plots determined by linear regression analysis. Protein was determined by the method of Lowry using bovine serum albumin as the protein standard.[11]

[^{125}I]iodocyanopindolol was obtained from New England Nuclear Medicine (Boston, Massachusetts). All other chemicals used were obtained from standard sources. Values of continuous variables are expressed as a mean ± standard deviation. Linear regressions by least squares were performed to obtain the relation of β-adrenergic receptor density and cardiac functional data. Ninety-five percent confidence limits were then obtained.

RESULTS

Myocardial beta-adrenergic receptors: Beta-adrenergic receptor density ranged from 34.3 to 93.7 fmol/mg protein (average 52.3 ± 18.0). Dissociation constants value ranged from 16.3 to 28.7 pM (average of 22.3 ± 4.3) (Table II).

Relation to New York Heart Association class: Beta-adrenergic receptor density in patients with functional class II to III congestive heart failure (58.7 ± 19.3 fmol/mg protein) was significantly higher ($p < 0.05$) than that in patients with class IV heart failure (37.1 ± 2.5) (Figure 1).

Relation to left ventricular function and other hemodynamic findings: Beta-adrenergic receptor density showed a positive linear correlation with end-systolic stress/end-systolic volume index ratio, the index for contractile function (Figure 2). On the other hand, β-adrenergic receptor density had no significant correlation with cardiac index, pulmonary artery wedge pressure and LV ejection fraction.

No significant relation was observed between dissociation constants for [^{125}I]iodocyanopindolol binding and each hemodynamic parameter evaluated in this study.

TABLE II Beta-Adrenergic Receptor Density and Dissociation Constant for [^{125}I]iodocyanopindolol Binding in Crude Membrane Prepared from Left Ventricular Papillary Muscle

Pt.	Receptor Density (fmol/mg protein)	Dissociation Constant (pM)
1	70.9	19.5
2	57.8	24.6
3	62.3	25.6
4	46.1	17.4
5	93.7	21.3
6	40.0	17.8
7	38.9	16.3
8	38.1	28.7
9	34.3	24.2
10	40.2	28.5
Mean ± SD	52.3 ± 18.0	22.3 ± 4.3

SD = standard deviation.

DISCUSSION

There have been several studies on myocardial β-adrenergic receptor density in patients with end-stage cardiomyopathy.[1–5] The degree of down-regulation has been related to the degree of heart failure, judged from clinical New York Heart Association classification. However, the status of β-adrenergic receptors has been less understood in valvular heart disease.[6–8] Furthermore, the relation between myocardial β-adrenergic receptor and cardiac function in these patients has been still obscure. The present study showed that in hearts with LV volume overload due to chronic valvular disease (1) myocardial β-adrenergic receptor density was less in patients with severe heart failure (New York Heart Association class IV) than in those with mild to moderate heart failure (class II to III); and (2) β-adrenergic receptor density had a good correlation with LV function, particularly with contractility.

In mitral valvular disease, β-adrenergic receptor density was reported to decline gradually when the degree of heart failure increased from functional class III to IV.[7,8] These studies have shown that down-regulation of the myocardial β-adrenergic receptor system has also occurred in valvular disease, and our result confirmed these results. From a functional viewpoint, cardiac index, pulmonary artery wedge pressure or LV ejection fraction had no significant correlation with β-adrenergic receptor, respectively. One of the reasons why we could not find any relation between them might be based on the unreliability of the aforemen-

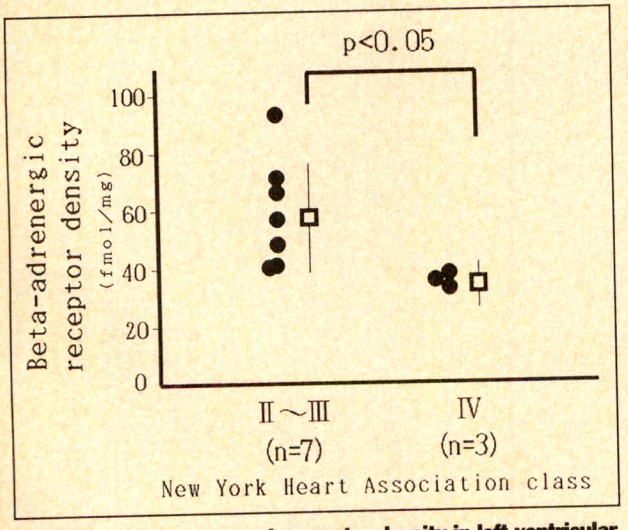


FIGURE 1. Beta-adrenergic receptor density in left ventricular papillary muscles from patients with chronic valvular disease in relation to the degree of heart failure (New York Heart Association class). Receptor density: fmol [^{125}I]iodocyanopindolol binding per milligram protein. Values are mean ± standard deviation.

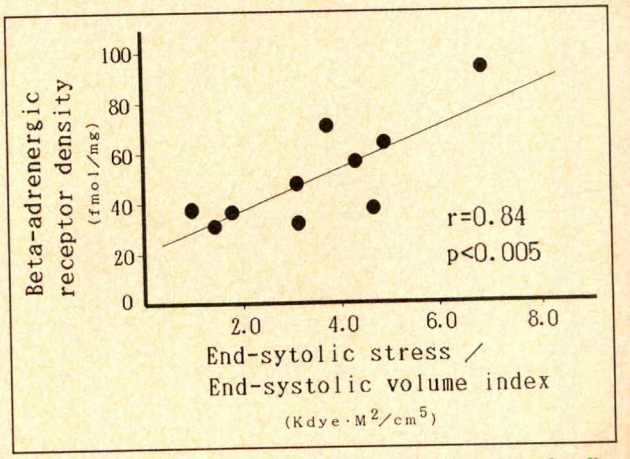


FIGURE 2. Correlation between β-adrenergic receptor density and end-systolic stress/end-systolic volume index ratio in patients with chronic valvular disease. Receptor density: fmol [^{125}I]iodocyanopindolol binding per milligram protein.

tioned indexes, because the aforementioned indexes are markedly influenced by many factors, such as loading condition or heart rate.

Recently, measurement of end-systolic stress/end-systolic volume index ratio has become available in the clinical setting. This is a very sensitive index for assessing myocardial contractility[12]; however, there are some limitations, e.g., size[13] and afterload[14] dependency. We found a positive correlation between end-systolic stress/end-systolic volume index ratio and myocardial β-adrenergic receptor density. Therefore, our results demonstrated that there was a good correlation between down-regulation of the myocardial β-adrenergic receptor and deterioration of LV contractility in LV volume overload hearts due to chronic MR with or without AR.

The precise mechanism of down-regulation of a myocardial β-adrenergic receptor in congestive heart failure is still obscure, and it was difficult to clarify the cause-and-effect relation between down-regulation of β-adrenergic receptor and contractile dysfunction in this study. Further study is needed for these unsettled questions.

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Echocardiographic Evidence for the Existence of a Distinct Diabetic Cardiomyopathy (The Framingham Heart Study)

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Although several reports have described early changes of cardiac structure and function in diabetic patients, controversy persists regarding the existence of a clinically distinct diabetic cardiomyopathy. To this end, sex-specific linear regression analyses were used to examine the contribution of diabetes mellitus and glucose intolerance to age-adjusted echocardiographic parameters in 1,986 men (mean age 48 years) and 2,529 women (mean age 50 years) from the original Framingham Study cohort and the Framingham Offspring Study. Subjects with evidence of cardiovascular disease at the time of echocardiogram were excluded. Diabetics had higher heart rates than nondiabetics (67.9 vs 64.0 beats/min ($p = 0.002$) in men, and 73.1 vs 68.3 beats/min ($p = 0.004$) in women). Diabetic women had increased left ventricular (LV) wall thickness (18.7 vs 17.1 mm, $p < 0.001$), relative wall thickness (0.403 vs 0.377, $p = 0.008$), LV end-diastolic dimension (46.9 vs 45.7 mm, $p = 0.03$) and LV mass corrected for height (100.4 vs 82.2 g/m, $p < 0.001$). Women with glucose intolerance showed similar, less significant trends ($p = 0.007$ for wall thickness, $p < 0.01$ for LV mass). In diabetic men, fractional shortening was slightly reduced (0.355 vs 0.360, $p < 0.05$). In a multivariate model that included potentially confounding factors, diabetes remained an independent contributor to LV mass ($p = 0.004$) and wall thickness ($p = 0.008$) in women. In a separate linear regression model, which assessed the association of age with LV mass, the age-coefficient for diabetic women was much higher than that for nondiabetics (13.6 vs 6.6 g/m per 10-year increment in age). In conclusion, many echocardiographic differences in diabetics are explained by the contributions of other concomitant factors such as obesity, hypertension and smoking, but an independent association of diabetes with LV mass and LV wall thickness is evident in women.

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Epidemiologic studies have clearly demonstrated that diabetic persons are at increased risk for cardiovascular morbidity and mortality.[1,2] Some investigators suggest that this is related to diffuse peripheral coronary atherosclerosis or unrecognized previous myocardial infarctions,[3] but others debate the actual mechanism.[2,4] In particular, risk for congestive heart failure is greatly increased in diabetes.[5] Furthermore, noninvasive studies have described early modifications of left ventricular (LV) structure and function in diabetics.[6,7] These findings have suggested the existence of a diabetic cardiomyopathy, which may be unrelated to coronary atherosclerosis.[8] Concomitant arterial hypertension was implicated in its development,[8] but recent echocardiographic studies did not find these abnormalities to correlate with elevated systolic blood pressure.[9,10] Despite the evidence of histopathologic and biochemical alterations of myocardium in diabetic animal models,[11–13] a demonstrable cardiomyopathy in human diabetics has remained difficult to establish. Thus, controversy persists regarding the existence of a distinct diabetic cardiomyopathy.[10,14] The present study examines LV structure and systolic function according to diabetic status of subjects enrolled in the Framingham Heart Study, who were free of clinically apparent cardiovascular disease.

METHODS

Study population: The study population consisted of men and women enrolled in the original Framingham Heart Study cohort and the Framingham Offspring Study. Selection criteria and study design have been previously described.[15,16] To be eligible for inclusion in study, subjects had to have adequate quality echocardiograms and be free of clinically apparent cardiovascular disease. Cardiovascular disease included coronary

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TABLE I Characteristics of the Study Subjects

Characteristics	Men (n = 1,986)	Women (n = 2,529)
Age (years)	48.2 ± 13.3	50.3 ± 14.5
Systolic blood pressure (mm Hg)	127.8 ± 16.6	123.6 ± 19.7
Diastolic blood pressure (mm Hg)	80.3 ± 9.2	75.6 ± 9.3
Heart rate (beats/min)	64.3 ± 10.7	68.6 ± 10.8
Body mass index (kg/m^2)	26.7 ± 3.6	25.0 ± 4.6
Hypertension* (%)	14.7	16.8
Antihypertensive treatment (%)	13.2	15.7
Cigarette smoking (%)	32.6	33.3
Diabetes (%)	3.5	1.7
Taking insulin (%)	0.5	0.4
Taking oral agent or on a diet (%)	2.9	1.3
Glucose intolerance (%)	12.2	5.5
Left ventricular hypertrophy (%)	13.9	16.1

*Hypertension is defined as blood pressure ≥160/95 mm Hg or those currently receiving drug treatment for hypertension.
Values are expressed as mean ± standard deviation.

TABLE II Age-Adjusted Parameters in the Selected Groups

	Nondiabetics	Subjects with Glucose Intolerance	Diabetics
	Men		
	n = 1,674	n = 243	n = 69
Heart rate (beats/min)	64.0	65.7*	67.9*
LV internal diameter-diastole (mm)	50.8	51.4*	51.0
LV internal diameter-systole (mm)	32.6	33.2*	33.0
Sum of LV wall thicknesses (mm)	19.5	19.7	19.9
LV mass/height (g/m)	112.3	115.8	116.9
Relative wall thickness	0.386	0.382	0.393
Fractional shortening	0.360	0.356	0.355†
	Women		
	n = 2,349	n = 138	n = 42
Heart rate (beats/min)	68.3	72.0‡	73.1*
LV internal diameter-diastole (mm)	45.7	46.0	46.9†
LV internal diameter-systole (mm)	28.2	28.4	28.9
Sum of LV wall thickness (mm)	17.1	17.7*	18.7‡
LV mass/height (g/m)	82.2	87.1*	100.4‡
Relative wall thickness	0.377	0.387	0.403*
Fractional shortening	0.383	0.383	0.385

*p <0.01; †p <0.05; ‡p <0.001.
LV = left ventricular.

artery disease (angina pectoris, coronary insufficiency, myocardial infarction), congestive heart failure, stroke or transient ischemic attack and intermittent claudication. Overt cardiovascular disease was identified through medical history, physical examination and hospital records. Criteria for the various cardiovascular disease events have been previously published.[17] Echocardiograms were not used to determine the presence or absence of cardiovascular disease.

From 1979 to 1983, echocardiography was routinely performed during the sixteenth biennial examination of the original cohort and during the second examination cycle of the offspring subjects. These examinations also included 12-lead electrocardiogram at rest, measurements of blood pressure at rest, anthropometric measurements and determination of blood glucose levels. Data regarding cigarette smoking and measurements of plasma total cholesterol and high-density lipoprotein cholesterol were obtained at the fifteenth biennial examination of the original cohort and the second examination of offspring subjects.

Diabetics were defined by the following criteria: a fasting whole blood glucose (Somogyi-Nelson) level ≥7.77 mmol/liter (140 mg/dl), a random nonfasting whole blood glucose level ≥11.11 mmol/liter (200 mg/dl), or the use of insulin or an oral hypoglycemic agent. Glucose intolerance was defined as a fasting whole blood glucose level ≥6.11 mmol/liter (110 mg/dl), a random nonfasting whole blood glucose level ≥6.66 mmol/liter (120 mg/dl), or the presence of glucose in the urine (definite or trace) in subjects who did not meet criteria for diabetes.

Echocardiographic methods: The echocardiographic methods used in the Framingham Heart Study have been previously described.[18] Subjects were studied using a standard M-mode echocardiographic technique. Measurements of the left ventricle were performed at end-diastole, according to both the American Society of Echocardiography recommendations[19] and the "Penn" convention.[20] LV mass was determined by the following equation used in conjunction with Penn convention measurements: LV mass (in grams) = 1.04 [(LVID + VST + PWT)^3 − (LVID)^3] − 13.6, where LVID = LV internal diameter, VST = ventricular septal thickness, and PWT = posterior wall thickness. LV mass (in grams) was corrected for height (in meters) as previously reported.[18]

Statistical analyses: Sex-specific linear regression analyses were used to examine age-adjusted echocardiographic parameters in nondiabetics, subjects with glucose intolerance and diabetics.

The associations of various potential confounding variables with echocardiographic parameters were examined for both men and women by a multivariate model that included age, heart rate, body mass index (calculated as the ratio of weight in kilograms to the square of height in meters), arterial hypertension (blood pressure ≥ 160/95 mm Hg or receiving antihypertensive treatment = 1; all others = 0), cigarette smoking (current smokers = 1; all others = 0), diabetes (yes = 1, no = 0) and glucose intolerance (yes = 1, no = 0).

TABLE III Unit Variations in Echocardiographic Parameters as a Function of Increments in Clinical Parameters*

	Age (×10 yrs)	BMI (×4 kg/m²)	HR (×10 beats/min)	SH (yes/no)	Cigarette Smoking (yes/no)	Diabetes (yes/no)	Glucose Intolerance (yes/no)
Men							
LV internal diameter-diastole (mm)	−0.59†	1.08†	−0.58†	0.31	−0.11	−0.12	0.23
LV internal diameter-systole (mm)	−0.59†	0.64†	−0.36†	0.10	0.11	0.29	0.36
Sum of LV wall thicknesses (mm)	0.53†	0.92†	−0.28†	0.79†	0.16	0.03	−0.31
LV mass/height (g/m)	3.92†	13.24†	−4.81†	9.00†	1.38	0.27	−2.16
Relative wall thickness	0.01†	0.008†	−0.0003	0.01‡	0.004	0.001	−0.008§
Fractional shortening	0.004‡	0.0004	−0.00009	0.001	0.003§	−0.005	−0.004
Women							
LV internal diameter-diastole (mm)	−0.63†	1.04†	−0.62†	−0.04	0.02	0.81	0.14
LV internal diameter-systole (mm)	−0.69†	0.76†	−0.40†	−0.12	0.06	0.33	0.05
Sum of LV wall thicknesses (mm)	0.83†	0.72†	0.01	0.62†	0.39†	0.92‡	0.31
LV mass/height (g/m)	5.15†	9.40†	−1.83†	5.54†	2.44‡	11.29†	1.29
Relative wall thickness	0.02†	0.004†	0.006†	0.01†	0.01†	0.01	0.003
Fractional shortening	0.006†	−0.024†	0.0003	0.0024	−0.0013	0.003	0.0002

*Regression coefficients derived from multivariate analysis of echocardiographic parameters adjusted for potential confounding variables.
†$p < 0.001$; ‡$p < 0.01$; §$p < 0.05$.
BMI = body mass index; HR = heart rate; LV = left ventricular; SH = systemic hypertension.

RESULTS

Study population: Of the 6,218 subjects who were seen at the index examination, 4,975 had technically adequate echocardiograms, and of these 4,516 were free of cardiovascular disease. The characteristics of the study population are listed in Table I. The mean age was 48 years in men and 50 years in women. Criteria for diabetes were fulfilled in 69 men (3.5%) and in 42 women (1.7%). Glucose intolerance was present in 243 men (12.2%) and in 138 women (5.5%).

Echocardiographic findings: The results of the age-adjusted analysis are listed in Table II. In both sexes, diabetes was associated with higher heart rate (67.9 vs 64.0 beats/min, $p = 0.002$, in men; 73.1 vs 68.3 beats/min, $p = 0.004$, in women). In diabetic women, there were increases in LV wall thickness (defined as the sum of ventricular septal and posterior wall thickness in millimeters) (18.7 vs 17.1 mm, $p < 0.001$), relative wall thickness (0.403 vs 0.377, $p = 0.008$), LV end-diastolic dimension (46.9 vs 45.7 mm, $p = 0.03$) and LV mass

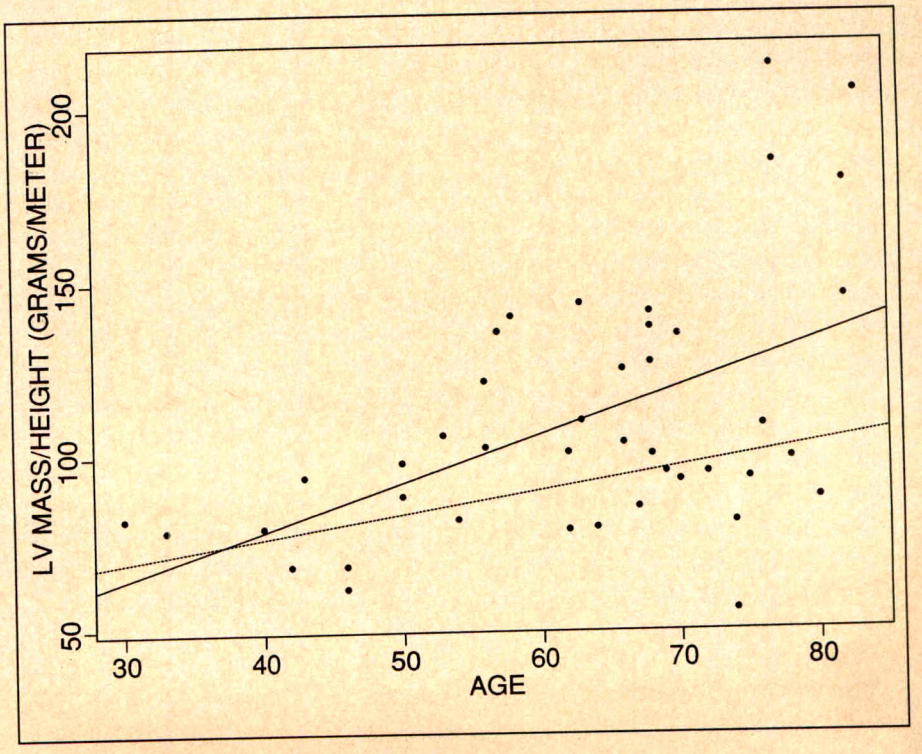


FIGURE 1. Echocardiographic left ventricular (LV) mass/height by age in diabetic women (n = 42) and in women with normal glucose levels (n = 2,349). Individual data points for diabetic women are presented. The regression line for diabetic women is depicted with a *solid line;* that for normal women is represented by a *dotted line.*

(100.4 vs 82.2 g/m, $p < 0.001$). Similarly, subjects with glucose intolerance had higher heart rates ($p < 0.01$ in men and $p < 0.001$ in women). In women with glucose intolerance, LV wall thickness ($p = 0.007$) and LV mass ($p < 0.01$) were increased compared with measurements in nondiabetics. Additionally, men with glucose intolerance had increased LV end-diastolic ($p < 0.01$) and end-systolic dimensions ($p < 0.01$).

Results from the multivariate model are reported in Table III. Diabetes remained independently associated with increased LV wall thickness ($p = 0.008$) and LV mass ($p = 0.004$) in women, with LV wall thickness 0.92 mm and LV mass 11.29 g/m greater in diabetic than in nondiabetic subjects. Glucose intolerance showed a slight inverse relation with relative wall thickness in men ($p = 0.03$). The inclusion in the multivariate model of diabetics taking insulin therapy ($n = 9$) versus noninsulin-dependent diabetics ($n = 33$) revealed independent contributions of both insulin-treated (regression coefficient = 20.49, $p < 0.002$) and noninsulin-treated diabetes (regression coefficient = 8.75, $p < 0.01$) to the level of LV mass in women.

Whether risk factors are associated with LV mass differently in diabetic than in nondiabetic women was examined by entering interaction terms between diabetes and risk factors in the multivariate model. The only term found to be significant was an age-interaction term ($p < 0.001$). Figure 1 shows the association of age with LV mass (corrected for height) in diabetic and nondiabetic women as estimated by separate linear regression models. The LV mass age coefficient in diabetic women is significantly higher than that estimated for nondiabetics (13.6 vs 6.6 g/m per 10-year increment in age). Thus, it appears that LV mass increases disproportionately with age in diabetic women.

DISCUSSION

In the 1974 Framingham Heart Study, investigators described the increased incidence of congestive heart failure in diabetic subjects.[5] Several studies have subsequently described a clinically definable diabetic cardiomyopathy.[8–10] Despite the use of powerful noninvasive techniques such as echocardiography and radionuclide ventriculography, controversy regarding the existence of a distinct cardiomyopathy in diabetics persists. The conflicting results of these studies may at least in part be due to disparity in patient selection, highlighting the importance of assessing well-defined diabetic populations and adjusting for the presence of potentially confounding variables such as age, obesity, hypertension and smoking.

The present study was designed to explore this controversy in a population-based sample free of overt cardiovascular disease. Furthermore, we also assessed subjects with glucose intolerance, creating an intermediate group between normal subjects and those with overt diabetes mellitus.

Similar to an earlier report,[21] age-adjusted analyses revealed differences in cardiac structure in diabetic women, with LV mass significantly higher than in control subjects. This was due to increased LV wall thickness. Women with glucose intolerance showed similar, less significant trends, strengthening the hypothesis of early changes of cardiac structure in the preclinical phase of impaired glucose metabolism. In contrast to previous studies, which did not show any change in LV systolic performance,[6,9,22] fractional shortening was slightly reduced in diabetic men.

Additional insights can be obtained from the multivariate model in which variables other than diabetes and glucose intolerance were introduced. The strong associations of hypertension and obesity with LV hypertrophy are well documented.[23–25] High blood pressure and overweight often coexist in diabetics[26]; thus, it is important to correct for these potential confounding variables in the multivariate model. The long-term influence of cigarette smoking on LV structure and function has not been thoroughly investigated, although a recent report has indicated unfavorable hemodynamic effects of acute exposure to smoking in patients with congestive heart failure.[27] Heart rate was included as an independent variable in the multivariate model because of its inverse relation with LV internal dimension, due to longer diastolic filling time occurring at slow heart rates. The higher heart rate found in diabetics in the present study is not surprising, probably secondary to cardiac vagal neuropathy.[28]

Multivariate analyses underscore the large contributions of obesity and hypertension to LV mass. An independent association of diabetes with LV mass and wall thickness was found in women but not in men. Previous pathologic and experimental studies in human and animal models have suggested elevated blood pressure to have a large role in the development of cardiomyopathy in diabetics.[8,22] In the present study diabetes showed a significant contribution to LV mass in women, which was slightly greater than the contributions of obesity and hypertension. No relation was found between diabetes and increased relative wall thickness, which is the echocardiographic expression of concentric hypertrophy induced by pressure overload.[29] These observations are consistent with the hypothesis that mechanisms other than increased afterload and overweight are involved in determining changes in cardiac structure of diabetic women. Interstitial deposition of para-aminosalicylic acid-glycoproteins and interstitial fibrosis described in diabetic hearts by pathology studies[11–13] might represent the basis of these changes.

Analyses performed by a distinct subdivision of diabetics according to therapy (insulin use or other treatments) revealed independent contributions of each subgroup to the level of LV mass in women. However, the size of the regression coefficient was substantially greater for diabetics using insulin, possibly reflecting the severity of metabolic disease.

The influence of age on LV mass in diabetic women was investigated by a separate linear regression analysis. In women with normal glucose levels we observed an expected, small increase in mean LV mass with advancing age.[24] In contrast, diabetic women had a substantially greater increment in LV mass with age, which was twice that observed in nondiabetic women. Younger diabetic women had no apparent increased LV mass. This result may reflect the cumulative impact of the duration of diabetes on the observed echocardiographic findings.

Why diabetes was associated with LV mass in women but not in men remains to be explained. The exclusion of subjects with overt cardiovascular disease may have blunted the extent of association between diabetes and cardiac changes in men by eliminating those most prone to heart involvement. However, it is remarkable that previous Framingham reports identified greater susceptibility of women to cardiovascular sequelae of diabetes and in particular to congestive heart failure.[2] The recent demonstration of a substantial link between echocardiographic determined LV hypertrophy and risk for major cardiovascular disease,[30] especially congestive heart failure, provides an anatomic basis for the incidence of cardiovascular disease complications in diabetic women. Even in the absence of systolic dysfunction, an impairment of diastolic relaxation, already described in the early phases of diabetes,[6,7,9,22] might underlie the occurrence of congestive heart failure in these patients. However, diastolic function was not assessed in the present study.

Further clinical studies directed toward defining the relations between diabetes, LV mass and diastolic function are needed. Our results suggest that much of the observed cardiac structural abnormalities in diabetics are explained by the coexistence of obesity and hypertension. However, based on evidence of an independent association of diabetes and increased LV mass, our findings support the hypothesis that a distinct diabetic cardiomyopathy exists in women.

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The Changing Pattern of Infective Endocarditis in Childhood

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Forty-eight cases of infective endocarditis (IE) that occurred in 42 patients with congenital heart disease were reviewed from 1970 through 1990 and were compared with a 20-year review of 108 cases diagnosed between 1953 and 1972. The review demonstrates that the natural history of IE in children has changed over the last 2 decades, with half of the cases occurring after surgery for congenital heart disease. In the postoperative group, 46% of patients had undergone valve replacement and 7 of these (29%) had a right ventricular to pulmonary artery valved conduit as the site for IE, suggesting significant additional risk in this setting. Among patients with nonsurgically treated congenital heart disease and IE, mitral valve prolapse has emerged as an important underlying heart lesion occurring in 29% of patients. The bacterial spectrum has shifted, with a significant increase in the incidence of uncommon causative organisms. Mortality has continued to decline with survivorship of 90% in this series.

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Infective endocarditis (IE) remains an important cause of morbidity and mortality in children with congenital heart disease. Extensive progress in surgery for congenital heart disease introduced in the last 2 decades has dramatically improved survival and, subsequently, created a patient population at long-term risk for IE. To identify changes in the pattern of the disease process in childhood, we analyzed all cases of IE occurring in the last 20 years and compared the results with a previous 2-decade experience from Boston Children's Hospital published in 1975.[1]

METHODS

A retrospective analysis was conducted of all records of pediatric patients with IE admitted between 1970 and 1990. Hospital records were reviewed for clinical presentation, laboratory result, echocardiographic findings, intraoperative reports and autopsy findings. The diagnosis of IE was based on the clinical profile of fever, a new or changing heart murmur, splenomegaly, embolic manifestations, new-onset congestive heart failure, anemia, hematuria, and so forth, with positive blood cultures; or the same clinical picture was seen with negative blood cultures and positive response to antibiotic treatment ± pathologic evidence of IE at surgery or autopsy.

RESULTS

There were 48 episodes of IE in 42 patients. The mean age was 12 years (range 1 month to 32 years), and both sexes were equally affected. All 42 patients had preexisting heart disease. The patient population was divided into 2 groups: those with congenital heart disease not treated surgically and those with previous cardiac surgery (postoperative); there were 24 episodes in each group. Findings in the 2 groups are summarized in Table I.

Clinical spectrum: Findings at presentation were similar to those reported in other series of IE in childhood.[1–4] Only 5 episodes (10%) occurred in children aged <2 years, 4 of whom were in the postoperative group. The time from onset of symptoms to diagnosis was >2 weeks in 19 of 48 episodes (40%). Recurrent endocarditis was seen in 4 patients: 2 with 3 episodes each and 2 with 2 episodes. Predisposing events were

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TABLE I Clinical Spectrum and Outcome

	Unoperated n (%)	Postoperative n (%)	Overall n (%)
Underlying cardiac pathology	24 (100)	24 (100)	48 (100)
Findings at presentation			
Fever	22 (92)	18 (75)	40 (83)
New/change precordial murmur	6 (25)	4 (16)	10 (21)
Splenomegaly	14 (58)	11 (46)	25 (52)
Skin manifestations	12 (50)	6 (25)	18 (38)
Age <2 years	1 (4)	4 (17)	5 (10)
Onset <2 weeks before diagnosis	17 (71)	12 (50)	29 (60)
Recurrent attacks	2 (8)	4 (17)	6 (13)
Preceding events	11 (46)	16 (70)	27 (56)
Vegetation by 2-dimensional echocardiography	13/16 (81)	6/15 (40)	19/31 (61)
Positive blood cultures	22 (92)	21 (88)	43 (90)
Organisms isolated			
S. aureus	11 (46)	2 (8)	13 (27)
S. viridans	9 (28)	5 (21)	14 (29)
Other bacteria	2 (8)	11 (46)	13 (27)
Fungus	—	3 (13)	3 (6)
Clinical course			
Medical therapy only	17 (71)	19 (79)	36 (75)
Surgical intervention	7 (29)	5 (21)	12 (25)
Congestive heart failure	3 (13)	10 (42)	13 (27)
Major emboli	7 (29)	9 (38)	16 (33)
Early deaths	—	3 (13)	3 (6)
Late deaths	1 (4)	1 (4)	2 (4)
Survival	23 (96)	20 (83)	43 (90)

S. aureus = staphylococcus aureus; S. viridans = streptococcus viridans.

identified in 27 of 48 cases (56%). Unprotected dental work was identified in 5 (10%), open heart surgery within 6 months in 7 (15%) and skin infections in 11 (23%) represented the most common predisposing events.

Echocardiographic findings: Of the 16 patients diagnosed in the first decade of this series, 13 had an M-mode echocardiogram and only 1 of these was diagnostic for vegetations. In the second decade of the study when 2-dimensional echocardiography was routine in this institution, echocardiograms were recorded in 31 patients and were diagnostic of vegetations in 19 (61%). Sensitivity of echocardiography in patients without operation was 81% compared with 40% in the postoperative group. Transesophageal echocardiography was supportive of the diagnosis of IE seen on transthoracic echocardiography in 2 patients and was diagnostic of vegetations in 1 patient whose transthoracic echocardiogram was considered nondiagnostic.

Infective organisms: Blood cultures were positive in 43 of 48 episodes (90%). In the 5 cases of culture-negative endocarditis, the diagnosis was confirmed by postmortem examination in 2, intraoperative findings in 1, and by successful response to antibiotic treatment with typical clinical profile in 2. Overall, Staphylococcus aureus and Streptococcus viridans were each responsible for approximately 30% of cases. However, unusual organisms were much more common in the postoperative group where they were responsible for 46% of cases. There were 3 episodes of fungal endocarditis, all in the postoperative group.

TABLE II Comparison of Infecting Organisms Recovered from Blood Cultures in Both Series

Type	Previous Series[1] (1953–1972) n (%)	Current Series (1970–1990) n (%)
α strep.	44 (41)	14 (29)
S. aureus	33 (30)	13 (27)
Uncommon organisms*	16 (15)	16 (33)
No organisms recovered	15 (14)	5 (11)
Total	108 (100)	48 (100)

*This includes 3 patients with fungal infective endocarditis in the present series; there were no cases of fungal infective endocarditis in the previous series.
S. aureus = staphylococcus aureus; strep. = streptococcus.

The causative organisms in the contemporary series are compared with those reported from Boston in 1975 (Table II). Staphylococcus aureus was the causative organism in 30% of that series, a very similar percentage to the 27% in the current series. In contrast, α streptococcus was responsible for 41% of cases in the Boston series and only 29% in the present series. Of the 16 patients who were infected with uncommon pathogens, 3 had fungal endocarditis after surgery for congenital heart disease compared with no episodes of fungal endocarditis in the Boston series. Culture negative endocarditis occurred at a similar incidence in both series.

Clinical course: All patients were treated medically, and in most (75%) this was all that was necessary. In 12 patients, surgical intervention was required during acute therapy of endocarditis; there was no difference in the need for surgical intervention between the groups treated with and without surgery. Congestive heart failure occurred often in postoperative patients, with IE occurring in 42% compared with only 13% in the group without surgery. Major embolic events occurred in approximately one-third of patients in both groups. Death related to early infectious complications occurred in 3 patients (13%) in the postoperative group and 2 of these were considered medical failures. No early deaths occurred in the surgically treated group. One late mortality occurred in the medically treated group related to complications from progressive renal failure, and 1 death due to intractible congestive heart failure occurred in the postoperative group. Overall, survivorship was 90%.

In comparing the outcome with that of the previous series,[1] mortality declined significantly from 21 to 10%. In the Boston experience Staphylcoccus aureus IE was responsible for 11 deaths (48%); in the present series, no deaths occurred in patients with Staphylococcus

TABLE III Cardiac Pathology

	Current Series (1970–1990) n (% of total)	Previous Series[1] (1953–1972) n (% of total)
Unoperated	24 (50)	101 (94)
Aortic valve disease	9 (19)	13 (12)
Mitral valve prolapse	7 (15)	0
Ventricular septal defect	3 (6)	15 (14)
Tetralogy of Fallot	1 (2)	35 (32)
Endocardial cushion defect	1 (2)	0
Truncus arteriosus	1 (2)	0
Complex congenital heart disease	1 (2)	0
Congenital mitral regurgitation	1 (2)	0
Rheumatic heart disease	0	5 (5)
No heart disease	0	8 (8)
Other	0	24 (22)
Postoperative*	24 (50)	7 (6)
Aortic valve disease	6 (12)	0
Tetralogy of Fallot	9 (19)	0
Complex congenital heart disease	4 (8)	0
Endocardial cushion defect	2 (4)	0
Aorticopulmonary shunt	2 (4)	7 (6)
Truncus arteriosus	1 (2)	0
Total	48 (100)	108 (100)

*In 11 of the postoperative patients in the present series, a prosthetic valve was present: 9 had had bioprosthetic valves (7 in right ventricular-pulmonary artery conduits as part of tetralogy of Fallot repair, 1 in left ventricular apex-descending aorta conduit, 1 in tricuspid position with endocardial repair and 2 had mechanical valves (1 each in mitral and aortic positions).

aureus IE. The 3 early deaths from IE in the contemporary series occurred in cases of fungal endocarditis in the early postoperative period.

Cardiac pathology: All 42 patients had preexisting structural heart disease (Table III). In the 24 cases in the nonsurgically treated group, aortic valve disease was the most common underlying lesion accounting for 38% of cases. There were 3 patients with ventricular septal defect and 1 with tetralogy of Fallot in the nonsurgically treated group.

Seven patients in the group without surgery (6 female and 1 male patient) had isolated mitral valve prolapse as the underlying structural congenital heart defect. Their findings are shown in detail in Table IV. Four children were known to have mitral valve prolapse, confirmed angiographically in 1 and by echocardiography in 3. All 4 had auscultatory findings of nonejection click associated with a systolic murmur of mitral regurgitation in 3. Of the 3 patients who were not known to have mitral valve prolapse before their presentation with IE, none had known murmurs, but all had audible mitral insufficiency at the time of diagnosis. Six of the 7 patients with mitral valve prolapse had positive blood cultures. In the seventh patient with negative blood cultures, the diagnosis of IE on the prolapsed mitral valve was confirmed at autopsy. Patients with mitral valve prolapse and IE were significantly compromised, with early major complications in 5 of 7 patients. Three had progressive congestive heart failure, 1 of whom required mitral valve replacement; 1 patient had a major stroke consequent to cerebral embolization, and another developed acute renal failure from immune complex nephritis. There were no deaths in the acute phase but 1 child required urgent mitral valve replacement, 3 were left with moderate to severe mitral insufficiency, 1 had significant residual left hemiparesis, and 1 died from progressive renal failure after discharge following recovery from IE.

In the postoperative group, 9 of 24 patients (38%) had undergone repair of tetralogy of Fallot and 6 (25%) had undergone surgery for aortic valve disease. These 2 lesions accounted for more than two-thirds of the cases occurring after surgery for congenital heart disease. Valve replacement was part of the repair in 11 of 24 patients with postoperative IE; 7 had valved conduits between the right ventricle and pulmonary artery as part of tetralogy repair, 1 had a left ventricular apex to descending aorta conduit and another had a bioprosthetic tricuspid valve. The other 2 patients had mechanical valves, 1 in the aortic position and 1 in the mitral position. When combined, these 11 cases accounted for 46% of the IE episodes occurring after surgery for congenital heart disease.

Overall, of the 48 episodes of IE, aortic valve disease was the most common underlying lesion before or after

TABLE IV Clinical Profile of Infective Endocarditis in Children with Mitral Valve Prolapse

Year Diagnosed	Age (yr) & Sex	Known MVP/MR	New/Increased MR Murmur	Preceding Event	Echo. Diagnosis of Vegetation	Organism Recovered	Complication	Outcome
1972	17 F	+/+	↑	Vaginal delivery	None performed	S. viridans	0	Alive/mod. MR
1975	15 F	−/−	+	0	(0) M-mode	Hemophilus parainfluenzae	CHF/MR	Alive/severe MR
1979	8 M	−/−	+	0	(+) M-mode	S. aureus	Major renal embolus CHF/MVR	Alive/MVR
1980	12 F	−/−	+	Impetigo	(+) 2-D	S. aureus	CHF	Alive/mild MR
1981	11 F	+/−	0	0	(0) 2-D	S. aureus	0	Alive/mild MR
1981	12 F	+/+	↑	0	(+) 2-D	0	Renal failure	Died
1988	9 F	+/+	↑	Dental work	(+) 2-D	S. viridans	Cerebral emboli	Alive/residual left hemiparesis/mod. MR

CHF = congestive heart failure; 2-D = 2-dimensional; Echo. = echocardiography; mod. = moderate; MR = mitral regurgitation; MVR = mitral valve replacement; + = present; − = no information available; 0 = absent; ↑ = increased; other abbreviations as in Table I.

operation (31%), followed by surgically treated tetralogy of Fallot (21%) and unsurgically treated mitral valve prolapse (15%).

Preexisting heart disease in the Boston series[1] is also listed in Table III. In that series, 101 of 108 episodes occurred in patients with nonsurgically treated heart disease (94%) compared with 50% of cases in this series. Obviously this reflects changes in the surgical approach to congenital heart disease. In patients with heart disease and IE who did not undergo surgery between 1953 and 1972, tetralogy of Fallot accounted for 35% of cases followed by ventricular septal defect in 15%. This is in contrast to only 1 patient with tetralogy of Fallot and 3 patients with ventricular septal defect in this series who did not undergo surgery. Aortic valve disease was the underlying cardiac diagnosis in only 13% of the Boston series compared with 38% in this series. Mitral valve prolapse was the second most common underlying diagnosis in this review in children with congenital heart disease not surgically treated (29%), whereas in the Boston series, there was no patient diagnosed as having mitral valve prolapse. Some of the 8 patients in the Boston series reported to have no significant heart disease or the 5 patients reported to have rheumatic mitral valve disease may have had mitral valve prolapse, since this diagnosis was not well recognized at that time. In this series, there was no patient with rheumatic heart disease. In the old series there were only 7 cases of IE in postoperative patients, all with aorticopulmonary shunts. This is in contrast to the 50% of patients who were postoperative in the current series, with only 8% with aorticopulmonary shunts.

DISCUSSION

Although IE remains an important cause of morbidity and mortality in children with congenital heart disease, this review is the first to indicate that important changes have occurred in the disease process in the last 2 decades. Studies of IE in adults have investigated the evolving nature of the disease with respect to changes in the underlying heart disease and infecting organisms.[5,6] This review shows that a parallel trend has occurred in pediatric IE. Increasing numbers of patients with congenital heart disease have undergone palliative and corrective surgery and represent a new group at risk for IE, whereas the pool of patients with nonsurgically treated congenital heart disease as a potential site for intracardiac infection has decreased. Reviews before 1960 reported that most of the patients with IE had rheumatic heart disease as the underlying lesion[1,2,7]; in the current series, no child with rheumatic disease developed endocarditis. In the Boston series,[1] almost all patients with congenital heart disease were not surgically treated; in the current series, half the patients with congenital heart disease underwent surgery; the 2 leading diagnoses in the Boston experience and other studies[1,2,3,8]—unoperated tetralogy of Fallot and ventricular septal defect—were only rarely seen in this current experience. Clearly, corrective surgery has resulted in a marked decline in the frequency of IE among such patients.

In contrast, mitral valve prolapse has emerged as a diagnosis predisposing to IE in childhood. In a review of 24 cases of IE in childhood between 1972 and 1982, 1 patient had mitral valve prolapse as the underlying lesion[4]; in a longitudinal study of 119 children with mitral valve prolapse between 1956 and 1977, 1 patient with IE was reported.[9] Numerous reports of IE on prolapsed mitral valve in adults identify mitral valve prolapse as a risk factor for IE.[10–16] In a prospective long-term follow-up of 300 adults with mitral valve prolapse between 1963 and 1983, 23 episodes of IE (15%) complicated the clinical course of the disease.[10] In other series, the incidence of IE is reported as 14 to 29%.[12–15] In general, mitral valve prolapse with mitral insufficiency is considered to represent a risk for endocarditis.[16–19] Unfortunately, it is well known that mitral insufficiency occurs intermittently in mitral valve prolapse and can therefore be missed clinically. Also, echocardiographic Doppler studies frequently indicate subclinical mitral insufficiency in association with mitral valve prolapse. Patients with endocarditis on a prolapsed mitral valve are subject to all the serious complications of left-sided intracardiac infection. When the diagnosis of mitral valve prolapse is made in childhood, it may well represent a patient with a more structurally abnormal valve. Our series suggests that careful consideration should be given to the subject of endocarditis prophylaxis in children with a diagnosis of mitral valve prolapse, even without consistent mitral insufficiency.

Among patients with IE after previous surgery for congenital heart disease, almost half of our cases occurred in patients who had undergone valve replacement; one-third of these occurred in patients with right-sided valve replacement including 7 with bioprosthetic valves in right ventricular to pulmonary artery conduits. In the adult experience, patients with prosthetic heart valves have been clearly identified to be at increased risk for endocarditis.[20–22] No previous review has indicated this propensity in children, particularly in those with right-sided valved conduits. As complex congenital heart diagnoses undergo repair, such surgical procedures will continue to increase in frequency. This review suggests that patients with right-sided valved conduits after repair of congenital heart disease are at particular risk for IE.

The study also indicates that there have been changes in the spectrum of causative organisms. There has been a significant increase in endocarditis caused by uncommon microorganisms, which are actually re-

sponsible for the majority of cases in this series. A similar observation was recently reported from the experience at Cleveland and the Mayo Clinic.[4,23] The increase in IE due to uncommon organisms parallels the increase in cases occurring after surgery for congenital heart disease. It is clear that cases of Streptococcal endocarditis have not decreased, but cases of endocarditis caused by unusual pathogens, including fungi, have increased after surgery for congenital heart disease. These findings emphasize the need for careful microbiologic screening when any clinical suspicion of endocarditis arises and raise questions about the use of routine preoperative antibiotic prophylaxis.

Before the antibiotic era, IE was uniformly fatal.[1,2] Reviews of IE in childhood have shown a continuous decline in the mortality rate,[1,3,4] and this series shows a further improvement to 90% survivorship for cases diagnosed in the past 2 decades.

Conclusion: The pattern of childhood IE has changed over the last 2 decades; in children with nonsurgically treated heart disease, mitral valve prolapse has become the second most common site for IE. Children who have undergone cardiovascular surgery for congenital heart disease now represent an important group at risk for IE, and this series indicates that those with right-sided valved conduits are at particular risk. A new bacterial spectrum has evolved with a significant shift toward uncommon pathogens, particularly in postoperative patients. The review emphasizes the importance of considering the diagnosis of IE in all patients with congenital heart disease both before and after surgery when the clinical setting for endocarditis is present.

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Abnormal Left Ventricular Diastolic Filling in Eccentric Left Ventricular Hypertrophy of Obesity

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Left ventricular (LV) diastolic filling pattern of obese subjects with eccentric LV hypertrophy was studied. Findings were compared with those of normal control subjects and hypertensive patients with concentric LV hypertrophy. M-mode, 2-dimensional and Doppler echocardiograms were recorded in 11 obese (body mass index >30 kg/m^2) normotensive patients with eccentric LV hypertrophy, 10 normal control subjects, and 18 nonobese, hypertensive patients with concentric LV hypertrophy whose antihypertensive medications were discontinued 2 weeks before study. LV hypertrophy was defined as LV mass/height >143 g/m. Hypertrophy in the obese patients was eccentric: Their LV internal dimension (61 ± 3 mm) was greater than that of hypertensive patients (55 ± 5 mm, p <0.001) and normal control subjects (55 ± 2 mm, p <0.01); their septal (10.7 ± 0.7 mm) and posterior (10.9 ± 0.6 mm) wall thicknesses were smaller than those of the hypertensive patients (12.2 ± 1.7 mm, p <0.05 and 11.7 ± 1.2 mm, respectively, difference not significant). Pulsed-wave Doppler echocardiographic filling indexes were used to evaluate LV diastolic filling. Obese patients had a higher peak velocity of atrial filling (69 ± 14 vs 54 ± 15 cm/s, p <0.05), lower early/atrial filling velocity ratio (1.0 ± 0.26 vs 1.32 ± 0.21, p <0.05), prolonged deceleration half-time (108 ± 9 vs 86 ± 15 ms, p <0.01) and lower peak filling rate corrected to stroke volume (4.08 ± 0.68 vs 4.96 ± 0.88 stroke volume/s, p <0.05) than normal control subjects. The deceleration half-time of obese patients correlated with the body mass index (r = 0.62, p <0.05). LV filling parameters of obese patients were not significantly different from those seen in hypertensive patients, except for a prolonged deceleration half-time corrected to heart rate (137 ± 22 vs 117 ± 19 ms, p <0.05). Eccentric LV hypertrophy of obesity causes an abnormal LV diastolic filling pattern similar to concentric LV hypertrophy of hypertension. Studies of LV diastolic function should take this variable into consideration.

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Echocardiographically determined left ventricular (LV) hypertrophy is an independent risk factor for coronary artery disease.[1] Epidemiologic data have implicated both hypertension and obesity as common risk factors for LV hypertrophy.[2] These 2 disorders, however, exert disparate effects on the cardiovascular system. Hypertension causes concentric hypertrophy (increased LV wall thickness with normal or decreased chamber volume) and obesity causes eccentric hypertrophy (LV chamber dilatation with normal or mildly increased wall thickness).[3] Many studies have shown that the concentric hypertrophy of hypertension results in abnormal diastolic function.[4] However, not all forms of hypertrophy cause abnormal diastolic function. Highly trained athletes with physiologic hypertrophy have normal diastolic function.[5,6] This study evaluates LV diastolic filling in subjects with eccentric LV hypertrophy due to obesity, and compares these parameters with those of normal control subjects and hypertensive patients with concentric LV hypertrophy.

METHODS

Patients: There were 3 groups of subjects. Group O consisted of 11 obese normotensive subjects with echocardiographic LV hypertrophy. These subjects had no hypertension at the time of the study or in the past. Obesity was defined as body mass index (weight in kg divided by height in m^2) >30 kg/m^2.[7] Among 20 obese subjects identified from an obesity-weight reduction clinic and other clinical services, adequate echocardiograms were feasible in 11. None of the obese patients were heavily-muscled athletes.

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TABLE I Clinical and Echocardiographic Features in Normal Controls, Obese Normotensive (group O) and Nonobese Hypertensive Patients (group H)

	Control	Group O	Group H	F
No. of subjects	10	11	18	
Age (years)	53 ± 13	52 ± 14	60 ± 8	1.5
Heart rate	69 ± 7	75 ± 10	63 ± 14*	4.2
BP, systolic (mm Hg)	133 ± 8	132 ± 10	148 ± 10†	12
BP, diastolic (mm Hg)	80 ± 4	80 ± 92	99 ± 3†	65
Body mass index (kg/m^2)	25 ± 2	35 ± 5†	27 ± 2†	30
Septum (mm)	9.1 ± 0.8	10.7 ± 0.7*	12.2 ± 1.7*	19
Posterior wall (mm)	9.1 ± 0.8	10.9 ± 0.6†	11.7 ± 1.2	23
LV dimension (mm)	55 ± 2	61 ± 3‡	55 ± 5†	11
Fractional shortening	0.34 ± 0.09	0.39 ± 0.07	0.36 ± 0.09	0.8
LV mass (g)	215 ± 37	342 ± 36†	330 ± 60	22
LV mass index (g/m)	123 ± 20	219 ± 30†	188 ± 33*	30

*p <0.05; †p <0.001; ‡p <0.01.
Symbols in group O indicate significant difference from control, and in group H significant difference from group O.
BP=blood pressure; LV=left ventricular.

Fifty patients with mild essential hypertension (diastolic blood pressure 95 to 104 mm Hg) were studied after their antihypertensive drugs were discontinued for 2 weeks. Among these patients, 18 with LV hypertrophy and no obesity (body mass index <30 kg/m^2) formed group H. These patients signed an informed consent approved by the Research and Development committee of the Miami Veterans Administration Medical Center. Exclusion criteria for all study subjects included: ischemic heart disease diagnosed by symptoms; pathologic Q waves on electrocardiogram or segmental wall motion abnormality on echocardiogram; congestive heart failure; heart rate <50 or >90 beats/min; first-degree heart block or any rhythm other than sinus; insulin-dependent diabetes mellitus; asthma or chronic obstructive lung disease; and valvular disease seen on physical and Doppler examination. Normal control subjects (n = 10) were of similar age, were not obese (body mass index <30 kg/m^2), met all of the aforementioned exclusion criteria, and underwent complete echocardiographic and Doppler studies which were normal; they were selected from patients referred for echocardiography and found to have no evidence of heart disease.

Echocardiography: The echocardiographic examination was performed with a Hewlett-Packard (model 7020A) imaging system. Complete M-mode, 2-dimensional and pulsed-wave Doppler studies were performed. The Doppler beam was aligned so that the angle between the ultrasound beam and the blood flow vector was as close to zero as possible. The sample volume was positioned at the level of the mitral anulus, between the mitral leaflets as they open in diastole. Doppler velocity curves were recorded on videotape or strip chart at 100 mm/s. Velocity curves from 5 cycles were traced with an off-line computer system. M-mode echocardiographic measurements were obtained according to the guidelines of the American Society of Echocardiography.[8] LV mass was calculated by the Penn cube method, described by Devereux et al.[9] LV hypertrophy was defined as LV mass/height >143 g/m.[2]

The peak of the initial velocity representing the early filling phase (E), and late filling phase (A) representing the atrial contraction, were measured by previously described methods.[10] The ratio of E/A filling velocity (E/A ratio) was calculated. The acceleration half-time (time for the early flow velocity to reach its peak from half the peak value) and deceleration half-time (time for the early flow velocity to decrease from its peak to half the peak value) were measured by previously described techniques.[11] Peak filling rate normalized to mitral stroke volume was derived by using the following formula described by Bowman et al[12]: peak filling rate = early peak filling velocity of mitral inflow (centimeters per second) divided by the time velocity integral (mean velocity multiplied by diastolic filling time).

Statistics: Data are reported as mean ± standard deviation. Statistical analysis was performed with a commercially available software (GraphPad-Instat) package. One-way analysis of variance was used to assess the significance of differences among means between groups. Adjusted *t* tests were performed and p values were corrected by the Bonferroni method. Corrected p values <0.05 were considered significant. Linear regression was used to assess the correlation between groups of data in each patient group.

RESULTS

Clinical and echocardiographic features of the patients in the 3 groups are listed in Table I. There was no significant difference in the mean age between the groups. Every patient in group O and H had LV hypertrophy. LV internal dimension was greater in group O. Doppler-derived LV filling parameters are listed in Table II. Compared with normal control subjects, patients

n group O had higher peak velocity during atrial filling, lower E/A filling velocity ratio, prolonged deceleration half-time, and lower peak filling rate corrected to mitral stroke volume. These abnormal diastolic filling parameters in group O were similar to those seen in group H, except for the rate-corrected deceleration half-time, which was prolonged.

When linear regression was used, the filling parameters were correlated to body mass index and LV mass index. The only significant correlation was between body mass index and deceleration half-time ($r = 0.62$, $p < 0.05$). The LV mass index did not correlate with the deceleration half-time.

TABLE II Left Ventricular Filling Parameters

	Control	Group O	Group H	F
Velocity E (cm/s)	72 ± 18	68 ± 13	58 ± 14	3.4
Velocity A (cm/s)	54 ± 15	69 ± 14*	65 ± 14	3.4
E/A ratio	1.32 ± 0.21	1.0 ± 0.26*	0.92 ± 0.35	6.0
AHT (ms)	43 ± 14	33 ± 10	43 ± 20	1.5
AHT/RR	50 ± 21	40 ± 12	42 ± 13	1.2
DHT (ms)	86 ± 15	108 ± 9†	106 ± 20	6.4
DHT/RR	96 ± 19	137 ± 22‡	117 ± 19*	11
PFR (SV/s)	4.96 ± 0.88	4.08 ± 0.68*	3.46 ± 0.6	15

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Symbols in group O indicate significant difference from control and in group H significant difference from group O.
A = atrial filling: AHT = acceleration half-time; DHT = deceleration half-time; E = early filling; PFR = peak filling rate; RR = R to R interval; SV = stroke volume.

DISCUSSION

Obesity is usually defined as the presence of an abnormally large amount of adipose tissue, and several methods are available for its diagnosis.[7] Obesity was diagnosed by the commonly used body mass or Quetelet index (kg/m^2), which has been used in many other studies.[2,7,13] A body mass index of ≥27.8 kg/m^2 was used to define obesity,[13] which corresponds to 120% of desirable weight.[7] All obese patients in this study had a body mass index >30 kg/m^2, which is considered to be moderate risk obesity.[7] Body mass index of the hypertensive patients was higher than the control but the difference did not reach statistical significance; this difference is due to the close association between obesity and hypertension.[3,14] The obese patients in this study were not hypertensive at the time of the study and did not have a past history of hypertension. There was no significant difference in mean age between the 3 groups.

LV mass was calculated by the Penn cube method.[9] Criteria for LV hypertrophy were based on mean values ± 2 standard deviations for LV mass and LV mass/height, derived from a study of a large number of healthy adults.[15] It is customary to correct LV mass by body surface area. However, when studying the effects of obesity it is preferable to correct LV mass to height.[2]

Unlike the hypertensive patients who had concentric LV hypertrophy, the obese patients had eccentric hypertrophy. This finding has been reported by other investigators.[3,16,17] In this study, obese subjects had prolonged deceleration time, higher peak velocity of atrial filling, and lower E/A ratio, compared with control subjects. These abnormalities suggest abnormal relaxation of the left ventricle with increased dependence on left atrial contraction for filling.[10,18] Hypertensive patients had similar abnormalities. Unlike hypertension, obesity causes an increase in intravascular volume, LV filling pressure, cardiac output and lower peripheral resistance. The increased intravascular volume would mask the Doppler-derived abnormalities of diastolic filling.[18] It is particularly interesting that an abnormal filling pattern was seen despite hemodynamics being unfavorable to its detection.

Although the effect of obesity on cardiac function has been studied,[19] to our knowledge, this is the first report demonstrating abnormal LV diastolic filling pattern in eccentric hypertrophy of obesity. A correlation between overweight and both LV diastolic pressure and amplitude of the A wave in the pulmonary wedge pressure tracing is seen in normotensive men.[20] Recently, Egan et al[21] reported that the peak filling rates of hypertensive patients was not significantly different from those of normotensive control subjects when age and weight were matched. Their patients did not have LV hypertrophy and the relative body weight correlated significantly with peak filling rates. In this study, the deceleration half-time correlated with body mass index, but the peak filling rate did not. Lavie et al[22] demonstrated left atrial enlargement and reduced left atrial emptying index in obese patients, indicating diastolic LV dysfunction.

Study limitations: The number of obese subjects studied is small and the findings need to be confirmed in a larger number of subjects. Coronary artery disease was not excluded by angiography. Although Doppler echocardiography is frequently used to evaluate diastolic function, diastole is a complex phenomenon and transmitral flow velocity pattern may be insufficient for its complete evaluation. The possibility that obesity without LV hypertrophy may cause abnormal LV diastolic filling was not addressed since all obese subjects in this study had LV hypertrophy.

Whereas concentric LV hypertrophy of hypertension is associated with abnormal diastolic filling and increased cardiovascular risk, eccentric hypertrophy of endurance athletes is not. This study shows that the eccentric hypertrophy of obesity results in an abnormal Doppler-derived diastolic filling pattern. The clinical significance of this finding is not known. Future studies of obesity and LV filling should take this variable into consideration.

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Effects of Handrail Support on Claudication and Hemodynamic Responses to Single-Stage and Progressive Treadmill Protocols in Peripheral Vascular Occlusive Disease

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Because handrail support reduces the energy cost of treadmill walking, claudication and hemodynamic responses of patients with peripheral vascular occlusive disease should also be affected. Furthermore, the reliability of the test results may be reduced unless the same pressure is applied to the handrails over repeated tests. The effect of handrail support on claudication and hemodynamic responses, and on their reliability, were examined during single-stage (2 mph, 12% grade) and progressive (2 mph, 0% grade with 2% increase every 2 minutes) treadmill protocols. Ten patients with stable disease performed both protocols 3 times, separated by 1 week, with and without handrail support. Claudication pain distance and maximal walking distance were greater ($p < 0.05$) when handrail support was permitted, and they increased ($p < 0.05$) over repeated tests of each protocol. No increase was noted over the tests without support. The responses and reliability of foot transcutaneous oxygen tension, ankle systolic pressure and ankle/brachial systolic pressure index after exercise to maximal tolerable pain were not affected by handrail support. Because claudication distances were altered, it is concluded that handrail support should not be allowed when assessing claudicants, unless balance cannot otherwise be maintained.

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The severity of peripheral vascular occlusive disease is clinically assessed by such performance-related measurements as the distance walked before the onset of claudication pain and the maximal walking distance,[1–4] and by such hemodynamic variables as foot transcutaneous oxygen tension,[5–9] ankle systolic pressure,[10–14] and the ankle/brachial index (ankle systolic pressure/brachial systolic pressure).[15–17]

A practical concern when measuring these claudication and hemodynamic variables is whether handrail support should be allowed. It has been found that submaximal oxygen consumption and heart rate are lower in healthy young men[18,19] and in patients with myocardial infarction[20] while walking using front handrail support than when no support was allowed. Furthermore, the magnitude of these reductions was directly proportional to the amount of tension applied to the handrail.[19] Thus, claudication and hemodynamic measurements of patients with intermittent claudication may also be affected. Furthermore, unless the same pressure is applied to the handrails over repeated tests, the reliability of these measurements may be reduced.

Because it is unclear whether the influence of handrail support is protocol-specific, the purpose of this investigation was to examine its effect on the claudication and hemodynamic responses, and on their reliability, during and following single-stage and progressive treadmill protocols.

METHODS

Patients: During an initial screening visit, patients with anginal symptoms, abnormal electrocardiographic patterns at rest or during exercise (ST-segment depression >1.0 mm [rest] and >2.0 mm [exercise], inverted T waves and arrhythmias), arthritis and diabetes were excluded from the study. Written informed consent was obtained from 10 patients with stable, but limiting, claudication pain for at least 1 year. Four patients had unilateral disease with arterial stenoses or occlusions present in either proximal ($n = 2$) or distal ($n = 2$) arteries. The remaining 6 patients had bilateral disease in the proximal arteries. Three patients currently smoked while the other 7 were former smokers. One

TABLE I Clinical Characteristics of 10 Claudicant Patients

Variable	M	SE
Age (years)	71	1.9
Weight (kg)	73	3.9
Ankle systolic pressure (mm Hg)	104	14.1
Brachial systolic pressure (mm Hg)	151	6.4
Ankle/brachial systolic pressure index	0.69	0.08
Brachial diastolic pressure (mm Hg)	75	3.2
Foot transcutaneous oxygen tension (mm Hg)	37	5.6
Heart rate (beats/min)	70	4.0

M = mean; SE = standard error.

patient had orthopedic discomfort in the hips that was secondary to claudication pain. None were taking medication for their claudication. The mean age, weight and hemodynamic variables of the group measured during supine rest in the more severely diseased leg and the right arm are listed in Table I.

Treadmill protocols: Each patient performed single-stage (2 mph, 12% grade) and progressive (2 mph, 0% grade with 2% increase every 2 minutes) treadmill protocols with and without handrail support. Three tests were done under each condition (i.e., single-stage + handrail support; progressive + handrail support; single-stage + no handrail support; progressive + no handrail support). A latin-squares randomized design was used for the order of the 12 performed tests, with approximately 1 week separating them.[21] The procedures used in this study were approved by the institutional review board for research involving humans.

Handrail support: Before each test with handrail support, patients were instructed to lightly touch the front handrail to maintain balance. Because they tended to grasp the handrail as claudication pain increased, patients were carefully observed throughout the test and were reminded to touch the handrail with their palms flat as the level of pain progressed.

Before each test without handrail support, patients were instructed to walk with their arms freely swinging. However, they were permitted to briefly touch the handrail during moments of instability and during the measurement of blood pressure. Additionally, patients held the handrail as they began walking until they became accustomed to the exercise (approximately 5 to 15 seconds). To ensure safety, 1 investigator stood behind the patients throughout each test and could stop the treadmill at any time.

Procedures: REST: Patients rested in the supine position for 20 minutes, after which foot transcutaneous oxygen tension, blood pressure and heart rate measurements were recorded. Foot transcutaneous oxygen tension values were obtained with a Novametrix Model 818 Transcutaneous Oxygen Monitor (Novametrix Medical System, Wallingford, Connecticut) and a Clark-type polarographic electrode placed on the dorsum of the foot. Ankle systolic pressure was taken from either the posterior tibial or the dorsalis pedis artery of the more diseased leg with a Versatone bidirectional Doppler (model D-9) and bidirectional probe (model P-92; 8 MHz). See previous reports for more detail.[3,22]

EXERCISE: After 3 minutes of standing, measurements were recorded to serve as a baseline for comparison with values obtained during exercise. During the treadmill tests, patients indicated when their claudication pain began and when they no longer could endure the pain. Foot transcutaneous oxygen tension, brachial blood pressure and heart rate were recorded at the claudication pain distance and the maximal walking distance.

RECOVERY: On completion of exercise, patients rested in the supine position while foot transcutaneous oxygen tension, blood pressure and heart rate were recorded at 1, 2, 4, 6, 8, 10, 12 and 15 minutes. All measurements of foot transcutaneous oxygen tension and ankle systolic pressure were taken by the same investigator at approximately the same time of day for each patient.

Statistical analyses: A 3-factor (treadmill protocol × handrail support condition × test) analysis of variance (ANOVA) with repeated measures was used to assess each claudication distance, and a 4-factor (treadmill protocol × handrail support condition × test × occasion) repeated-measures ANOVA was used to assess the hemodynamic variables measured at various occasions within each test (i.e., before, during and after exercise). Tukey tests were performed after each ANOVA to locate differences between means.[23] The reliability of each variable under each of the 4 treadmill protocol × handrail support conditions was assessed by an intraclass correlation coefficient (mean square between − mean square within/mean square between) obtained from a 1-factor (test) repeated-measures ANOVA,[24,25] and the coefficient of variation (standard deviation/mean) of the repeated measure.[25] Statistical significance was set at $p < 0.05$.

RESULTS

Claudication responses: Although some patients demonstrated between a 1- and 2-mm depression of their ST segment during exercise, none experienced angina. All treadmill tests were terminated because maximal claudication pain was attained. A significant handrail support condition × test interaction ($p < 0.05$) was demonstrated for both the claudication pain distance and the maximal walking distance (Figure 1). Values were higher and increased over repeated tests during both protocols with handrail support, whereas no change was noted over the tests without support. Handrail support minimally reduced the intraclass correlation coefficients of the claudication variables during either protocol, except for claudication pain distance dur-

ing the single-stage protocol (Table II). The coefficients of variation were lowest for maximal walking distance during the progressive protocol with and without handrail support.

Hemodynamic responses: Values for foot transcutaneous oxygen tension, ankle systolic pressure, brachial systolic pressure, ankle/brachial index and heart rate were pooled across the 2 handrail support conditions and the 3 repeated tests because these factors were not significant (Figures 2 to 6). A treadmill protocol × occasion interaction existed for each variable ($p < 0.05$), because values were similar between the 2 protocols until supine recovery. Heart rate demonstrated a different pattern than the other variables in that differences were noted between the protocols during exercise as well as during recovery. Brachial diastolic pressure remained relatively constant during all of the various treadmill tests (data not shown).

The intraclass correlation coefficients (Table III) and the coefficients of variation (Table IV) for foot transcutaneous oxygen tension, ankle systolic pressure and ankle/brachial index were similar between handrail conditions and between treadmill protocols. The reliability values of brachial systolic and diastolic pressures and heart rate were also similar between handrail conditions and between treadmill protocols (data not shown).

TABLE II Reliability of Claudication Responses During Repeated Walking Tests

	R		CV (%)	
Protocol	CPD	MWD	CPD	MWD
Single-stage				
Handrail	0.48	0.85	31	28
No handrail	0.75	0.88	22	20
Progressive				
Handrail	0.76	0.94	33	17
No handrail	0.82	0.96	22	11

CPD = claudication pain distance; CV = coefficient of variation; MWD = maximal walking distance; R = intraclass correlation coefficient.

DISCUSSION

The main findings of this investigation were that claudication distances were greater when handrail support was permitted and they increased over repeated single-stage and progressive tests, indicating a reduced reliability. In contrast, the responses and reliability of each hemodynamic variable were not affected by handrail support.

Claudication responses: COMPARISON BETWEEN TREADMILL PROTOCOLS: Claudication pain results from an inadequate blood flow to meet the metabolic demand of exercising muscle. Because the imbalance between blood flow and metabolic demand becomes greater as exercise intensity increases, it is not surprising that the claudication pain variables occurred sooner during the single-stage protocol. Indeed, patients would have needed to walk to the seventh stage (13 to 14 minutes) during the progressive protocol to achieve an equal exercise intensity. These results support earlier work, because the claudication distances during a different single-stage protocol (1.5 mph, 7.5%) occurred sooner than during the progressive protocol.[22]

EFFECT OF HANDRAIL SUPPORT: During both treadmill protocols, claudication pain distance and maximal walking distance were greater when claudicants lightly

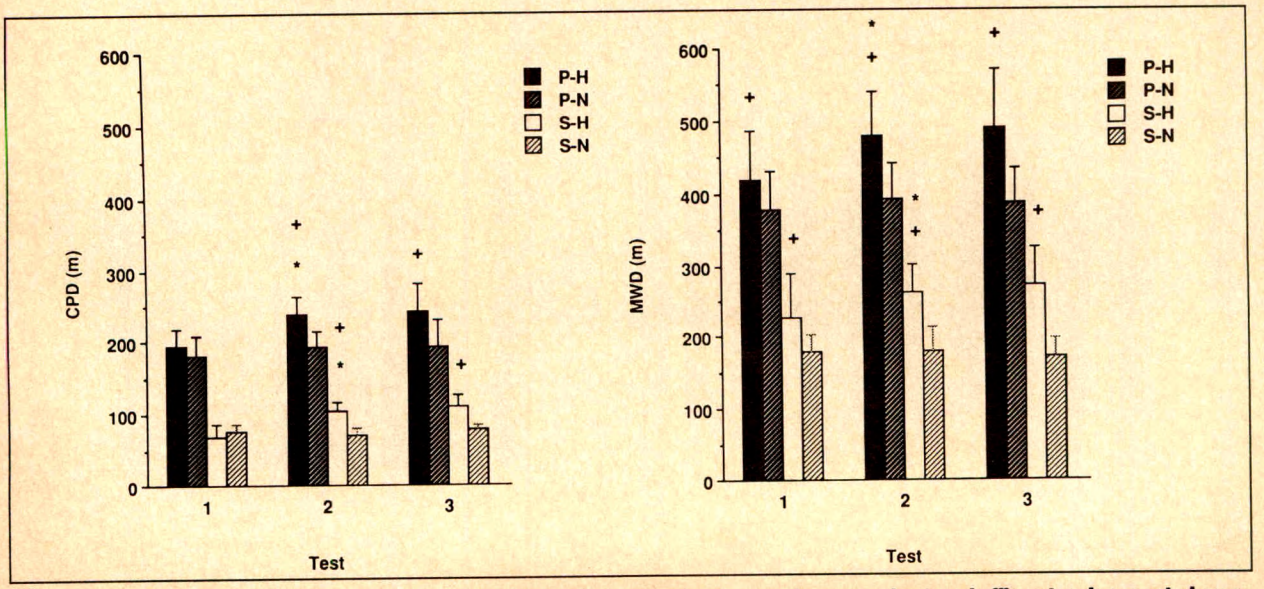


FIGURE 1. Claudication distances (meters) of 10 patients during single-stage and progressive treadmill protocols repeated over 3 tests with and without handrail support. Values are means ± standard error of the mean. CPD = claudication pain distance; H = handrail support; MWD = maximal walking distance; N = no handrail support; P = progressive protocol; S = single-stage protocol; * = significantly greater than the preceding test ($p < 0.05$); + = significantly greater than the N condition ($p < 0.05$).

touched the handrail with their palms flat than when no support was permitted. This suggests that spuriously high claudication distances are obtained while walking with handrail support. Consequently, the degree that claudication pain limits the performance of routine physical activities would be underestimated. These results are in agreement with the findings of Zeimetz et al,[19] who found that the mean treadmill time to attain 85% of predicted maximal heart rate in healthy young men was progressively lengthened as the amount of horizontal tension applied to a handrail apparatus was increased. The enhanced treadmill performance was attributed to a flatter increase in slope of heart rate and oxygen consumption with progressively greater exercise intensity.[18,19] Haskell et al[20] found similar results in patients who had had myocardial infarction, as the maxi-

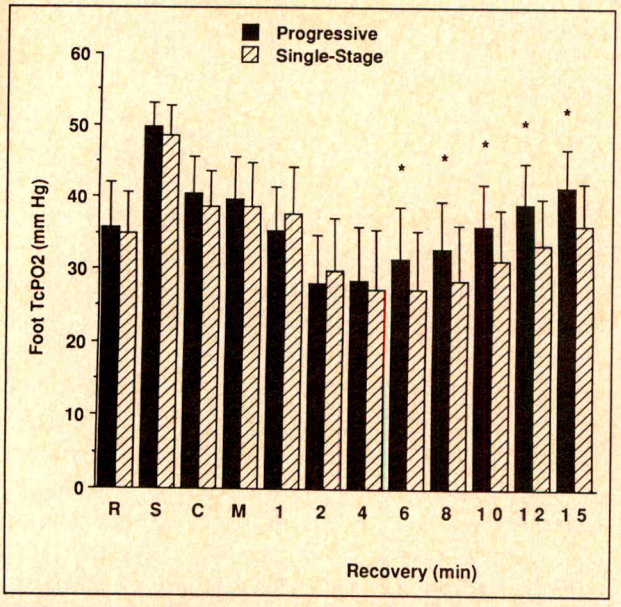


FIGURE 2. Foot transcutaneous oxygen tension of 10 claudicants before, during and after walking. Values (mean ± standard error of the mean) were pooled across the 2 handrail conditions and across the 3 repeated tests. C = claudication pain distance; M = maximal walking distance; R = rest; S = standing; TcPO2 = transcutaneous oxygen tension; * = significant difference between the 2 protocols ($p < 0.05$).

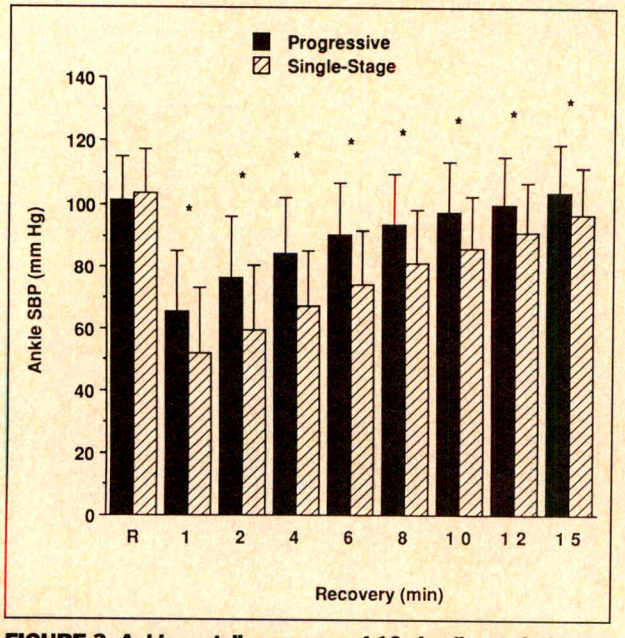


FIGURE 3. Ankle systolic pressure of 10 claudicants before and after walking. Values (mean ± standard error of the mean) were pooled across the 2 handrail conditions and across the 3 repeated tests. R = rest; SBP = systolic blood pressure; * = significant difference between the 2 protocols ($p < 0.05$).

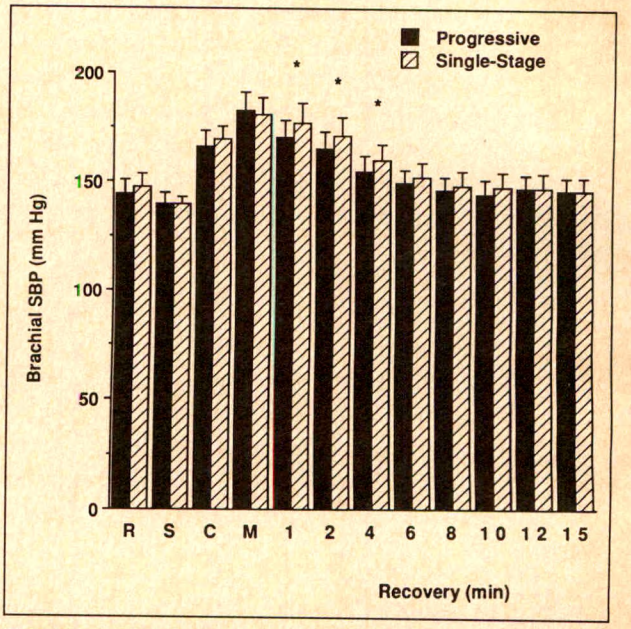


FIGURE 4. Brachial systolic blood pressure before, during and after walking. Values (mean ± standard error of the mean) were pooled across the 2 handrail conditions and across the 3 tests. Abbreviations as in Figures 2 and 3.

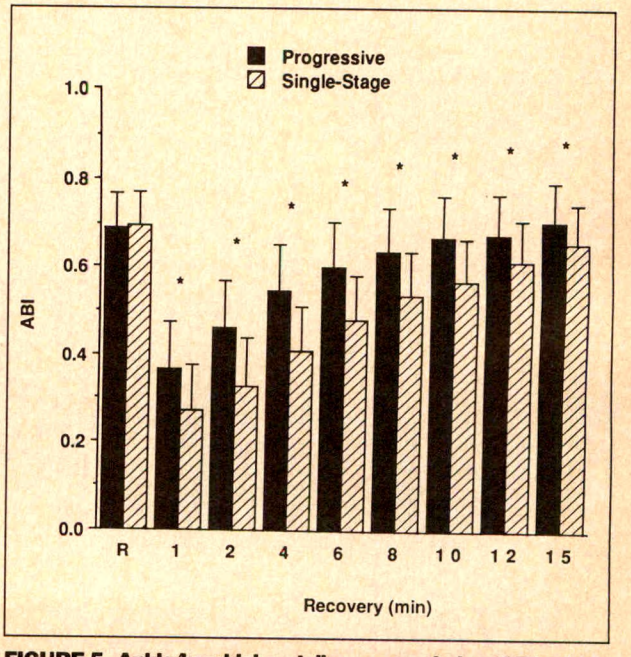


FIGURE 5. Ankle/brachial systolic pressure index (ABI) of 10 claudicants before and after walking. Values (mean ± standard error of the mean) were pooled across the 2 handrail conditions and across the 3 tests. R = rest.

TABLE III Reliability of Hemodynamic Variables of 10 Claudicants Before, During and After Repeated Walking Tests*

Variable/Condition	Occasion R	St.	C	M	Recovery
Foot TcPO2					
S-H	0.79	0.51	0.70	0.81	0.72-0.93
S-N	0.76	0.34	0.70	0.75	0.81-0.94
P-H	0.85	0.26	0.70	0.83	0.80-0.97
P-N	0.91	0.30	0.70	0.75	0.78-0.93
Ankle Systolic Blood Pressure					
S-H	0.98				0.97-0.99
S-N	0.98				0.92-0.98
P-H	0.98				0.97-0.98
P-N	0.96				0.94-0.96
Ankle/Brachial Index					
S-H	0.97				0.96-0.99
S-N	0.97				0.90-0.98
P-H	0.98				0.96-0.98
P-N	0.96				0.94-0.96

*Values are intraclass correlation coefficients.
C = claudication pain distance; H = handrail support; M = maximal walking distance; N = no handrail support; P = progressive protocol; R = rest; S = single-stage protocol; St. = standing; TcPO2 = transcutaneous oxygen tension.

TABLE IV Variability of Hemodynamic Variables of 10 Claudicants Before, During and After Repeated Walking Tests*

Variable/Condition	Occasion R	St.	C	M	Recovery
Foot TcPO2					
S-H	35	33	33	51	33-76
S-N	38	37	34	38	30-37
P-H	30	47	42	44	22-44
P-N	30	26	26	23	24-30
Ankle Systolic Blood Pressure					
S-H	11				11-28
S-N	9				10-22
P-H	8				10-27
P-N	13				10-20
Ankle-Brachial Index					
S-H	10				11-31
S-N	8				9-28
P-H	8				10-29
P-N	12				11-20

*Values are coefficients of variation (%).
Abbreviations as in Table III.

mal oxygen consumption predicted from submaximal heart rate was greater than the actual measured value when support was allowed.

RELIABILITY OVER REPEATED TEST: Handrail support minimally reduced the intraclass correlation coefficients of the claudication distances during either protocol, except for the claudication pain distance during the single-stage protocol. However, the mean value of the claudication pain distance and the maximal walking distance increased from the first to the second test. Thus, the ranking of claudicants according to their claudication values remained relatively constant, even though most patients increased their distances over repeated tests. Because a reliable measurement includes both a high intraclass correlation coefficient and no change in the mean over repeated trials,[24] claudication responses were less reliable during each protocol when handrail support was permitted. The coefficients of variation were presented to describe the amount of variation that should be expected in the claudication pain distance and the maximal walking distance in an average claudicant tested under each walking condition.

The lack of reliable claudication values when patients are allowed to lightly touch the handrail underscores the potential problem of research studies designed to observe changes over time after surgery, medication treatment or exercise training (i.e., a change in the claudication response to exercise may be attributable to a change in the dependence on handrail support rather than to an intervention). Measuring claudication pain without handrail support should therefore provide a truer estimate of the effect of a treatment (e.g., surgery, medication and exercise) on walking ability.

No patient had difficulty walking without support throughout this study. Thus, handrail support may be an unnecessary safety precaution for most patients with peripheral vascular occlusive disease as long as they are permitted to touch the handrail periodically to maintain balance.

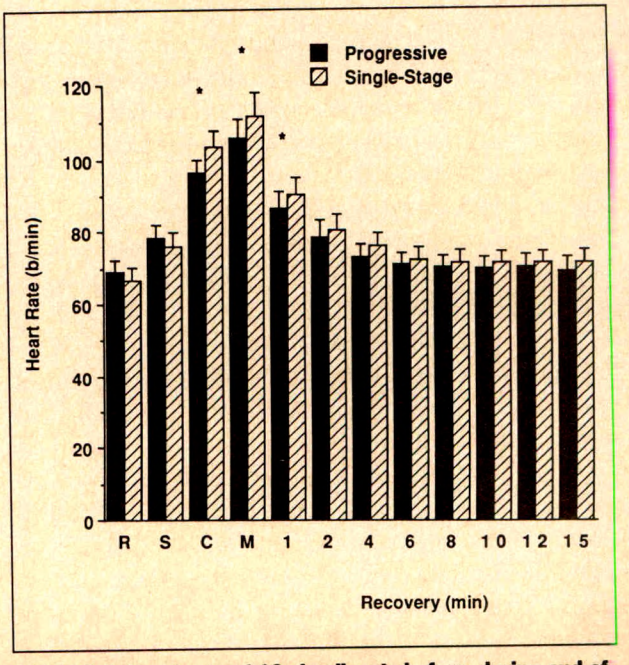


FIGURE 6. Heart rate of 10 claudicants before, during and after walking. Values (mean ± standard error of the mean) were pooled across the 2 handrail conditions and across the 3 tests. Abbreviations as in Figure 2.

Hemodynamic responses: AT REST AND DURING EXERCISE: The value of each hemodynamic variable measured at rest remained unchanged over the study, suggesting that there was no clinical evidence of disease progression. A typical decrease in foot transcutaneous oxygen tension during walking[5–7] was noted with both protocols, due to a decreased muscular vascular resistance that shunts the already compromised blood flow away from cutaneous tissue.[13] As previously reported[22] most of the reduction in foot transcutaneous oxygen tension during exercise occurred by the claudication pain distance. This suggests that the compromise in cutaneous blood flow during exercise occurs relatively soon in the distal region of the leg.

DURING SUPINE RECOVERY: Foot transcutaneous oxygen tension, ankle systolic pressure and ankle/brachial index declined below their resting baseline values because the vasodilatory stimulus was still present in the previously active ischemic leg muscles, and because of the reduction in cardiac output.[5,13] Additionally, values for each variable were even lower after the single-stage protocol, suggesting that a greater amount of metabolites may have accumulated because of the higher exercise intensity.[26] As the metabolites are cleared from the ischemic muscular tissue during recovery, the vasodilatory stimulus gradually subsides, increasing the peripheral circulation, which is manifested by an increase in foot transcutaneous oxygen tension, ankle systolic pressure and ankle/brachial index toward baseline. Typical responses of the central circulatory variables (brachial systolic and diastolic pressure, and heart rate) were noted during and after both treadmill protocols.

EFFECT OF HANDRAIL SUPPORT: The hemodynamic variables obtained at the claudication pain distance and the maximal walking distance in the present study were not affected by handrail support. The fact that the claudication variables were lengthened with support suggests that foot transcutaneous oxygen tension was higher, and brachial systolic and diastolic pressure and heart rate were lower at similar time intervals during tests using handrail support. Further examination of these exercise responses indicated that these trends did exist but were small in magnitude.

RELIABILITY OVER REPEATED TESTS: Handrail support did not alter the reliability of the hemodynamic variables during and after both protocols, as none of the variables demonstrated a change in mean throughout each test and all had high intraclass correlation coefficients. Thus, although patients walked longer with handrail support, they still stopped at their maximal level of tolerable pain, causing similar hemodynamic responses during and after exercise. The reliability values of foot transcutaneous oxygen tension, ankle systolic pressure and ankle/brachial index were comparable to those found in previous reports[22,27–29] and, with the exception of foot transcutaneous oxygen tension, were as reliable as brachial systolic and diastolic pressure and heart rate. Because great care was taken to calibrate the transcutaneous electrode and to prepare the skin on the dorsum of the foot, the lower reliability of foot transcutaneous oxygen tension (compared to ankle systolic pressure and ankle/brachial index) suggests that the microcirculation was more variable than blood flow through the dorsalis pedis or posterior tibial arteries.

Because claudication distances were altered, it is concluded that handrail support should not be allowed when assessing claudicants, unless balance cannot otherwise be maintained.

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Angiotensin-Converting Inhibitors in Patients with Congestive Heart Failure: A Class Effect?

Bertram Pitt, MD

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve exercise performance, patient well-being and survival in patients with heart failure.[1-4] Both captopril and enalapril have been approved for use in heart failure and it is likely that several other ACE inhibitors will be approved within the near future. Although they differ in duration of action and side-effect profile, it has generally been thought that one ACE inhibitor is equal to another in effectiveness.[5] This concept has now been challenged by Pouleur et al,[6] who found in a retrospective analysis of baseline therapy in the Xamoterol Mortality Trial that patients receiving baseline therapy with captopril had a significantly higher mortality than those receiving enalapril.

Pouleur et al postulate that the higher mortality of patients receiving captopril in their study was due to the fact that captopril's duration of action is shorter than that of enalapril. Because captopril is recommended to be used 3 times daily, compared with 2 times daily for enalapril in patients with heart failure, compliance may have been worse with captopril, thereby leaving patients exposed to the adverse effects of renin-angiotensin system activation. Furthermore, many investigators in their study administered captopril at a lower than recommended dose or on a twice-daily rather than a three-times daily schedule in order to reduce the cost of chronic therapy. However, one should be skeptical of any retrospective analysis such as that performed by Pouleur et al. Their trial was not designed, nor statistically empowered, to explore the relative difference in effectiveness between captopril and enalapril. Nevertheless, one cannot ignore the possibility that significant differences in the effectiveness of various ACE inhibitors might exist.

If differences in the effectiveness of ACE inhibitors do exist, how might they be explained? One explanation is that proposed by Pouleur et al.[6] Should the neuroendocrine hypothesis for heart failure prove to be valid—i.e., that activation of neurohormones, in particular the renin-angiotensin system, is important in determining survival in patients with heart failure—one could postulate that failure to provide adequate and continuous blockade of the renin-angiotensin system could lead to an increase in the incidence of manifest heart failure and death. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial of enalapril in patients with class IV heart failure, Swedberg et al[7] showed that enalapril was effective in reducing the incidence of progressive heart failure and mortality only in patients with marked activation of the renin-angiotensin system. The Veterans Administration Vasodilator Heart Failure Trial-II (VHEFT-II) comparing a strategy of direct-acting vasodilators with isosorbide dinitrate-hydralazine to an ACE inhibitor strategy with enalapril has shown that enalapril was more effective in reducing mortality (Cohn J, personal communication). The reduction in mortality with enalapril in the VHEFT-II occurred despite the fact that the isosorbide dinitrate-hydralazine combination appeared to be the more effective vasodilator, as evidenced by a greater improvement in left ventricular ejection fraction and exercise performance. The improved mortality with enalapril in both the CONSENSUS trial and the VHEFT-II is therefore likely due to the fact that it is an inhibitor of the renin-angiotensin system rather than a pure vasodilator.

Other explanations for a potential difference in the efficacy of captopril and enalapril can also be postulated. Toussaint et al[8] showed in a study of human volunteers that there may be significant differences in the effectiveness of loop diuretic-induced natriuresis with different ACE inhibitors. They compared the natriuretic effect of furosemide alone and after pretreatment with 3 ACE inhibitors: 100 mg of captopril, 5 and 10 mg of ramapril, and 20 mg of enalapril by mouth. In those pretreated with captopril, there was significantly less natriuresis than with ramapril or enalapril. They found that captopril interfered with the delivery of furosemide to the distal renal tubule and, hence, natriuresis. In patients with heart failure, a relative decrease in effective diuresis and natriuresis with 1 ACE inhibitor

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versus another could lead to a higher incidence of salt and water retention, manifest heart failure, and further activation of neurohormones, thereby leading to the well-known vicious cycle of heart failure. Although their study needs to be confirmed and repeated in patients with heart failure, it does raise the possibility that there may be important differences among the various ACE inhibitors.

The possibility that the major effects of ACE inhibitors may not be through blockade of the serum angiotensin system, but rather through the tissue ACE system is even more intriguing.[9–11] The tissue ACE system has important effects on vascular and myocardial remodeling. Differences in lipophilicity and chemical structure among the various ACE inhibitors results in differential effectiveness in inhibiting ACE activity, in particular tissues and organs.[9–11] Whether or not the differential effects of various ACE inhibitors in specific organ systems are of importance needs to be determined by appropriate, prospective, well-controlled comparative studies.

There are also other differences that need to be considered relative to the clinical effectiveness of various ACE inhibitors. Captopril has, in contrast to enalapril, a sulfhydryl (SH) group. Although this was originally thought to be a disadvantage due to the side effects inherent to the SH group, recent studies have suggested that the SH group could be an asset. Captopril prevents the oxidation of catecholamines and has been shown to be more effective than enalapril in protecting against myocardial stunning.[11–14]

What can the clinician infer from the study of Pouleur et al? First, I believe that we should continue to use both captopril and enalapril for heart failure therapy. Both have been shown to reduce the incidence of manifest heart failure and its consequences.[1–4,15] Captopril should, however, be prescribed only as recommended in the package insert, 3 times daily. The clinician should be wary of using any new ACE inhibitor or vasodilator in patients with heart failure based solely on evidence of benefit in another indication, such as hypertension, or comparability in improving exercise performance. Approval for use of an ACE inhibitor or vasodilator should not, in my opinion, be based on demonstration of an improvement in exercise performance alone without demonstration of a reduction in the incidence of manifest heart failure, if not mortality. Our knowledge of the pathophysiology of heart failure is as yet incomplete. The use of surrogate end points, such as exercise performance, which appear to depend on vasodilation for approval and clinical use of ACE inhibitors, although convenient, may not be justified. Although we want our patients to feel better and to exercise more, we also need to know that we can prevent the development of manifest heart failure, with all of its deleterious consequences and costs. Prevention of the development of manifest heart failure and improvement of survival may depend on completeness in blockade of the serum or the tissue renin angiotensin system, or both. Until we have greater understanding of these effects, it would be prudent to prescribe only ACE inhibitors that have been shown to prevent the development of manifest heart failure or improve survival, or both, and only in doses shown to be effective in the pivotal trials.

Before new ACE inhibitors or vasodilators are approved for use in heart failure, we need to have more data on the effective as well as the minimally effective dose. We still do not know the minimally effective dose of captopril or enalapril for preventing manifest heart failure and death. This may or may not be the same dose that blocks the serum renin-angiotensin system. If Poleur et al[6] are correct, many of our patients currently treated with ACE inhibitors may not be adequately protected.

The concept of class effectiveness is being challenged not only for ACE inhibitors, but also for β-adrenergic blocking agents. A recent study by Ablad et al[16] suggests that lipophilic β-adrenergic blockers might be more effective than hydrophilic β blockers in reducing sudden cardiac death.[16] Although both lipophilic and hydrophilic β-adrenergic blocking agents were equally effective in reducing heart rate and evidence of ischemia in their animal model, the lipophilic β blocker was more effective in reducing sudden death by increasing central vagal tone.

We need well-controlled, prospective, comparative trials to determine whether or not claims of class effectiveness are valid. It is possible that we may need to reevaluate our current concepts of class effectiveness in the light of new understanding of pathophysiology.

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Permanent Pacing as Treatment for Hypertrophic Cardiomyopathy

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The management of patients with hypertrophic cardiomyopathy (HC) is directed at 2 separate but interrelated goals: the amelioration of symptoms and the identification of those patients at risk of sudden cardiac death. Symptomatic improvement can be obtained in most patients with the use of standard pharmacotherapy.[1–3] Surgical intervention, either in the form of septal myectomy or mitral valve replacement, can be considered for those with obstructive disease who do not respond to medical therapy.[3–5] Septal myectomy and mitral valve replacement are successful procedures that lessen both the resting and provokable outflow tract gradient, reduce left ventricular end-diastolic pressure and result in significant symptomatic improvement.[4,5]

Unfortunately all of these treatments have disadvantages. Calcium antagonists are associated with major and minor side effects.[6] Verapamil may precipitate pulmonary edema, especially in patients with significant resting outflow tract gradients and a high left ventricular end-diastolic pressure.[6] Beta blockers in the doses prescribed often cause fatigue. Both groups of drugs may precipitate conduction disturbances.[6] Surgical myectomy and mitral valve replacement, although successful in relieving symptoms, have an operative mortality ranging from 3 to 16% and have not been shown to alter the natural history of this disease.[7,8]

Because of these difficulties, it is important to search for alternative management options, especially for patients with HC who are refractory to the aforementioned standard therapy. Several centers, including our own, have pioneered the use of atrioventricular sequential pacing in the management of these patients.[9–16] Pacing in these circumstances is being used to relieve symptoms and not to manage conduction system disease.

Hassenstein et al[9] were the first to describe this approach. They reported a 56% reduction in left ventricular outflow tract gradient during paced rhythm in 4 patients, all of whom reported symptomatic improvement. These findings were confirmed by Duch et al,[11] who observed similar hemodynamic results in a series of 21 patients. Twelve patients in this group had a reduction of ventricular outflow tract gradient of $\geq 50\%$ in paced rhythm. Only 1 patient did not achieve any reduction in gradient in paced rhythm. The reduction in gradient was associated with a decrease in left ventricular filling pressure. These hemodynamic responses were not associated with any significant reduction in mean arterial pressure. This response mirrors the hemodynamic outcome from surgical interventions in this condition. Similar findings have been reported by both Duport,[10] Gardiner[13] and their co-workers. Recently, preliminary data from the National Institutes of Health have shown a similar favorable hemodynamic and symptomatic response with pacing in this condition.[16]

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This early experience with pacing as a therapeutic intervention in HC indicates that improvement in symptomatic status can be achieved. We have recently documented both a subjective and objective improvement in functional status in 11 patients with HC who were paced because of refractory symptoms.[12] The objective improvement in functional status was demonstrated by improved treadmill times during paced rhythm compared with sinus rhythm. These exercise tests were performed during a time period 4 to 24 months after pacemaker implantation. Similar symptomatic benefit has been documented by other investigators.[9,13,16] The mechanism explaining this beneficial response is unknown. Several investigators have shown that pacing can reduce the resting left ventricular outflow tract gradient in this condition.[9–11,13,16] Although the pathophysiologic significance of the outflow tract gradient in HC remains unclear, its reduction by pacing may well explain the symptomatic improvement seen with this intervention. The mechanism behind this hemodynamic response is unknown. Pacing from the right ventricle alters the sequence of left ventricular activation. This may result in paradoxical motion of the ventricular septum, thereby widening the outflow tract area and reducing the Venturi forces on the anterior leaflet of the mitral valve. This proposed widening of the left ventricular outflow tract by right ventricular pacing has yet to be demonstrated. In fact there are no data available on the effect of pacing on left ventricular cavity size or outflow tract size in this condition. Alternatively, outflow tract gradient may be reduced as a result of the less vigorous left ventricular contraction induced by paced rhythm, reducing both the velocity of flow and the resultant Venturi forces acting on the anterior mitral valve leaflet. Data from Duch et al[11] show some reduction in the first derivative of left ventricular pressure during paced rhythm in this condition. Irrespective of the mechanism, the data are clear that ventricular pacing does reduce the left ventricular outflow tract gradient, and is associated with a reduction in left ventricular end-diastolic pressure.[11]

Although there appears to be general agreement in available publications that pacing can reduce the outflow tract gradient, the effect of this intervention on ventricular diastolic function remains unclear. We have documented symptomatic improvement in some patients with no significant resting outflow tract gradient.[12] However, no physiologic maneuvers were performed on this group to ascertain whether a provokable gradient was present. Accordingly, the symptomatic improvement in those patients may still have been due to a reduction in provoked gradient during exercise in a manner analogous to the beneficial effect of myectomy or mitral valve replacement in patients with no resting but a documented provokable gradient. Alternatively, pacing may have an independent beneficial effect on diastolic function. Preliminary data from our center supports this concept,[15] but more work is needed to investigate the effect of pacing on diastolic function in this condition.

Atrioventricular as opposed to ventricular pacing has been our choice of pacing mode for this intervention in HC. This decision was based on the fact that atrial transport may be of critical importance and therefore ventricular pacing on its own may compromise the patient's condition. However, 1 of our patients developed refractory atrial fibrillation 3 years after the insertion of a dual chamber pacing unit. Atrioventricular nodal ablation was eventually required to control ventricular rate. This patient continued to be well symptomatically with single chamber ventricular pacing until her recent death from a noncardiac cause.

To date, no significant adverse effects have been reported with this intervention. Ventriculoatrial conduction could be a problem with dual chamber pacing in HC as a potential initiating factor for pacemaker-mediated tachycardia. However, it is our experience that by prolonging the atrial refractory period, ventriculoatrial conduction can be blocked in most cases. Ventriculoatrial conduction intervals, however, should be checked after alterations in concomitant medical therapy, because drugs frequently used in the medical management of HC are known to prolong this interval.[17] Other than the potential for pacemaker-mediated tachycardia, there appears to be little arrhythmogenic potential with this intervention.

Apart from programming the atrial refractory period to ensure blockade of ventriculoatrial conduction, the other pacing parameter of major interest in this application of pacing is the atrioventricular conduction interval. Maintaining this interval shorter than the physiologic atrioventricular delay is of paramount importance in efforts to ensure ventricular capture at all times, especially during exercise. We have achieved this by programming atrioventricular delay intervals short enough to maintain paced ventricular rhythm during maximal treadmill exercise,[12] resulting in the routine programming of intervals ranging between 50 and 100 ms. Using pacing units with a rate-responsive atrioventricular delay will obviously simplify this problem. Aside from the need to maintain ventricular capture, it is unclear whether there is an optimal atrioventricular delay for this intervention. Von Bibra et al[18] stressed the effects of varying atrioventricular intervals during paced rhythm on the length of the left ventricular filling period in other clinical settings. Their results demon-

strated that shorter intervals were associated with longer left ventricular filling periods over the range of atrioventricular intervals assessed. Our preliminary data confirmed this finding by demonstrating improved and prolonged ventricular filling at an atrioventricular delay of 50 ms when compared with 150 ms in patients with HC.[15]

In summary, several investigators have now demonstrated that dual chamber pacing is an effective form of therapy for patients with obstructive HC. The documented reduction in outflow tract gradient and left ventricular filling pressure associated with symptomatic improvement are findings comparable to those achieved with myectomy. Its effect on diastolic function in this condition requires further study. Because of the significant morbidity and mortality of the surgical approach in this condition, it is reasonable to suggest that dual chamber pacing should be actively considered as a therapeutic option, especially for patients being evaluated for surgery.

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Effects of Beta$_2$-Adrenoceptor Stimulation on Exercise-Induced Myocardial Ischemia

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In large epicardial coronary arteries, β_2 adrenoceptors represent only 15% of the total population of β adrenoceptors.[1] Thus, their stimulation is unlikely to affect coronary blood flow significantly.[2] Conversely, in small coronary arteries, β_2 adrenoceptors represent 93% of the total population of β adrenoceptors.[1] Their stimulation causes vasodilation.[2] Experimental studies, however, have shown that β_2-adrenoceptor-mediated vasodilation of small coronary arteries is more pronounced in subepicardial than in subendocardial layers, thus provoking a reduction of the endo/epicardial flow ratio.[3] As the subendocardium is more susceptible to myocardial ischemia than the subepicardium,[4] this redistribution of coronary blood flow toward the subepicardial layers, in the presence of critical coronary stenoses, might reduce the ischemic threshold during exercise. Furthermore, stimulation of β_2 adrenoceptors in the sinus node, recently demonstrated in humans,[5] might increase the heart rate, thus reducing exercise duration. We investigated the clinical importance of the detrimental consequences of β_2-adrenoceptor stimulation in a trial of the effects of salbutamol on exercise-induced myocardial ischemia in patients with stable angina pectoris. The confounding influence of β_1-adrenoceptor stimulation was prevented by pretreatment with atenolol. Furthermore, to establish whether nonselective β-adrenoceptor blockade is able to prevent these detrimental effects, salbutamol was given to another group of patients after pretreatment with propranolol.

Sixteen patients (13 men and 3 women, aged 41 to 78 years, mean 61) with stable effort angina pectoris (symptom duration ranging from 15 to 72 months, mean 42), an exercise test positive for angina and myocardial ischemia (horizontal or down-sloping ST-segment depression >1.5 mm) and documented coronary artery disease (internal diameter reduction >70% of ≥1 major branch) participated in this study. All patients had reproducible positive exercise tests. Coronary angiography showed 1-vessel disease in 2 patients, 2-vessel disease in 8 patients and 3-vessel disease in 6 patients. Four patients had had a previous myocardial infarction >18 months before the study. All patients were normotensive, in sinus rhythm and without evidence of heart failure, cardiomyopathy, valvular disease, diabetes mellitus and pulmonary disease. No patient had evidence on the electrocardiogram of left ventricular hypertrophy or conduction defects, which might have interfered with the interpretation of ST-segment changes, and no patient was receiving digitalis. All patients were familiar with the exercise protocol and medical environment before the study. Written informed consent was obtained from all patients before entry into the study, which had been approved by the Hammersmith Hospital Ethics Committee.

Nitrates other than sublingual nitroglycerin, calcium antagonists and β-blocking agents were withdrawn 4 days before entry into the study. Patients were then randomly assigned to receive either oral atenolol (100 mg/day) (8 patients) or propranolol (40 mg 4/day) (8 patients). After 1 week of treatment, patients underwent a randomized, single-blind, placebo-controlled, crossover trial of the effect of salbutamol on exercise capacity. Salbutamol (500 μg in 10 ml of saline) or placebo (saline) was infused via an antecubital vein over a period of 10 minutes in 2 consecutive days. Arterial blood pressure (cuff sphygmomanometer) was obtained immediately before the infusion, at 1-minute intervals during the infusion and at the end of the infusion. Within 2 minutes of the end of the infusion, patients underwent a symptom-limited, computer-assisted (CASE Marquette 12) treadmill exercise test using the modified Bruce protocol. A 12-lead electrocardiogram and arterial blood pressure were recorded immediately before the test, at 1-minute intervals during exercise, and each minute up to 10 minutes after exercise. Three electrocardiographic leads were continuously monitored before, during and after exercise. All exercise tests were performed at the same time of day, between 2 and 4 hours after the last dose of atenolol or propranolol (Figure 1). For each exercise test, the level of the ST segment 60 ms after the J point was calculated after signal averaging by a computer-assisted system in all 12 leads every minute. This provided measurements of the ST-segment level with an accuracy of 0.1 mm. The lead revealing

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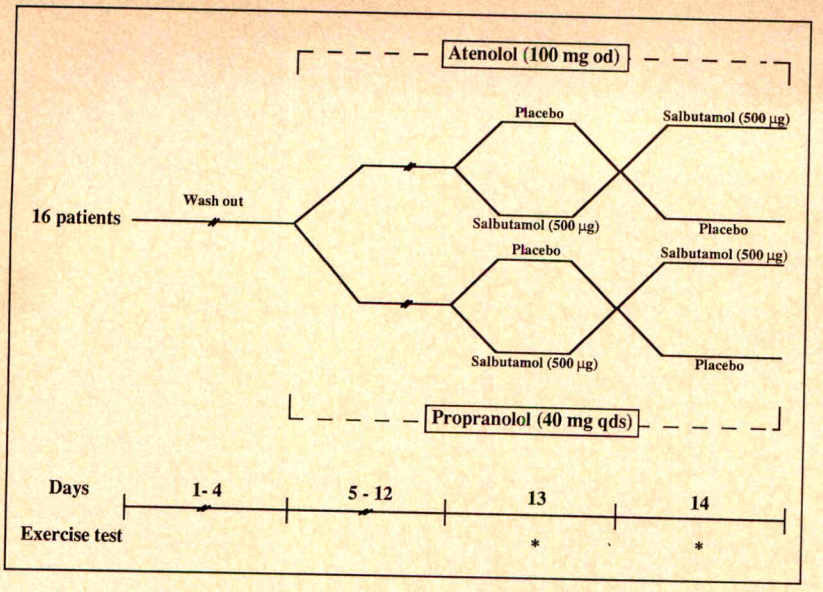


FIGURE 1. Diagrammatic representation of study design. After a 4-day washout phase, patients were randomly assigned to receive either atenolol (100 mg/day) or propranolol (40 mg 4/day) for 7 days. Then patients randomly underwent exercise test after infusion of placebo or salbutamol in a 2-day crossover study (*days 13 and 14).

the greatest ST-segment depression was selected for analysis. The following parameters were then measured: (1) time, in seconds, to the onset of 1-mm ST-segment depression; (2) heart rate, blood pressure and heart rate/blood pressure product at the onset of 1-mm ST-segment depression, and (3) exercise duration, in seconds. The exercise tests were analyzed while blind to the treatment.

The statistical analysis of the results relative to the exercise test was performed using the Student's t *test for 2-sample paired data. A p value <0.05 was considered statistically significant. Data are presented as mean ± 1 standard deviation.*

All patients tolerated atenolol without any adverse effect. In 2 patients, salbutamol infusion was discontinued after administration of 350 µg because of an excessive increase in heart rate (>50 beats/ min). Two other patients had transient fine hand tremors. Heart rate and blood pressure before the infusion of placebo or salbutamol were similar. After salbutamol infusion, heart rate at rest was higher than after placebo infusion (p <0.005), whereas blood pressure did not change. After salbutamol infusion, heart rate and rate-pressure product at 1-mm ST-segment depression were similar to that found after placebo infusion (Figures 2 and 3), while time to 1-mm ST-segment depression and total exercise time were significantly shorter (p <0.03 and <0.05, respectively) (Figure 4).

Both propranolol and salbutamol were tolerated by all patients without any adverse effect. Heart rate and blood pressure were similar both before and after the infusion of placebo or salbutamol. After salbutamol infusion, heart rate and rate-pressure product at 1-mm ST-segment depression were similar to that found after placebo infusion (Figures 2 and 3), such as time to 1-mm ST-segment depression and exercise duration (Figure 4).

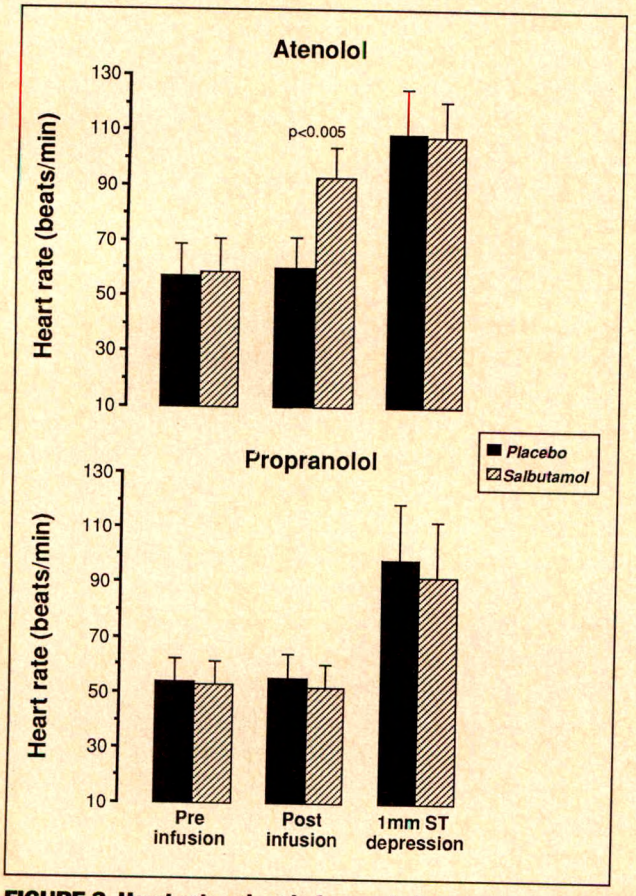


FIGURE 2. Heart rate values before and after placebo or salbutamol infusion and at 1-mm ST-segment depression in patients pretreated with atenolol *(top)* or propranolol *(bottom)*.

The results of this study show that, in humans, stimulation of coronary β_2 adrenoceptors by salbutamol does not reduce rate-pressure product (an index of myocardial

xygen consumption)[6] at the onset of exercise-induced ıyocardial ischemia. Therefore, differently from what as been observed in previous experimental studies, these esults indicate that coronary β_2-adrenoceptor stimula- on in humans is unlikely to impair coronary blood flow uring stress. However, β_2-adrenoceptor stimulation rovokes a marked chronotropic response that considera- ly reduces time to the onset of ischemia and exercise uration. This detrimental effect is prevented by pre- reatment with the nonselective β-blocking agent pro- ranolol. Because stimulation of β_2 adrenoceptors by atecholamines may occur during daily life, our results ndicate that, in patients in whom the control of heart ate is critical for the prevention of myocardial ischemia, he choice of nonselective blocking agents might be advis- ıble.

The theoretical possibility exists that an impairment f myocardial perfusion caused by selective salbutamol- nduced dilation of subendocardial small vessels might be counterbalanced by β_2-adrenoceptor-mediated vasodila- ion of epicardial vessels at the site of critical stenoses.[7] Indeed, the latter could increase distal coronary perfu- sion pressure, thus preventing the decrease caused by selective subepicardial vasodilation. However, this possi- bility seems to be rather remote, as experimental data show that, in different animal species, β_2 adrenoceptors on the smooth muscle of large coronary arteries represent only 15% of the total β-adrenoceptor population.[1] The possibility that the ischemic threshold during exercise in our patients was affected by stenosis constriction due to β-adrenoceptor blockade by atenolol or propranolol is also unlikely, as Bortone et al[8] in an angiographic study in humans recently demonstrated that β blockade does not increase stenosis severity during exercise.

A limitation of this study is the use of a single-blind design. However, the selection of objective end points (time to and heart rate-pressure product at 1-mm ST-segment depression during exercise testing), the computerized assessment of the electrocardiograms and the analysis of results while blinded to treatment should substantially overcome the drawbacks of the single-blind design.

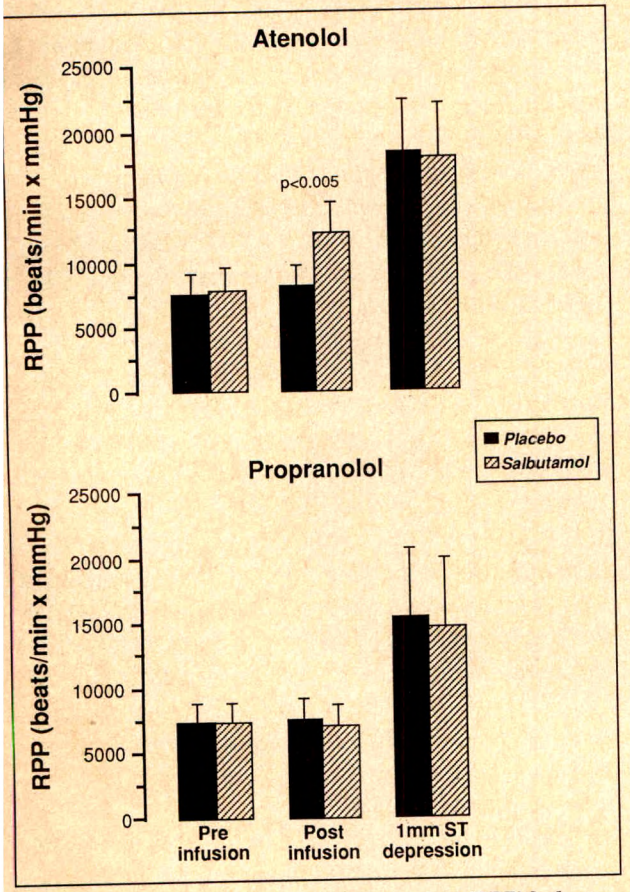


FIGURE 3. Heart rate/blood pressure product (RPP) before and after placebo or salbutamol infusion and at 1-mm ST-segment depression after placebo or salbutamol infusion in patients pretreated with atenolol *(top)* or propranolol *(bottom)*.

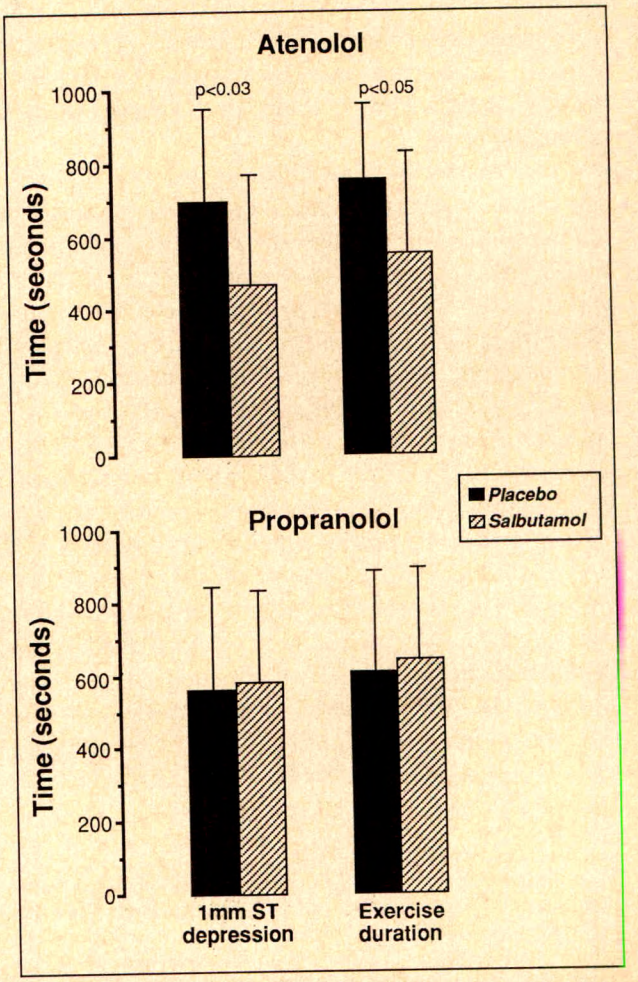


FIGURE 4. Time to 1-mm ST-segment depression and exercise duration after placebo or salbutamol infusion in patients pretreated with atenolol *(top)* or propranolol *(bottom)*.

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Effects of Percutaneous Transluminal Coronary Angioplasty on Exercise-Induced Changes in R-Wave Amplitude

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The prevalence of coronary artery disease and the availability of effective therapies create the need for a reliable screening test. Unfortunately, the predictive accuracy of exercise stress testing based on the development of symptoms or ST-segment depression is limited. This study assesses the validity of exercise-induced changes in R-wave amplitude as an index of myocardial ischemia.

Nine patients with isolated left anterior descending coronary artery disease who underwent successful percutaneous transluminal coronary angioplasty (PTCA) are included in this analysis. Upright treadmill stress testing was performed according to a modified Naughton protocol on the same day as the radionuclide study, 24 to 72 hours before and after PTCA. Modified bipolar precordial leads CM^1 and CM^5 were monitored. R-wave amplitude was measured from the isoelectric line to the peak of the QRS complex using handheld calipers and averaged over 10 to 20 beats. R-wave measurements were taken at rest and at maximal exercise before PTCA. After PTCA, measurements were taken at rest, at the heart rate equivalent to maximal exercise before PTCA and at the new peak exercise. Multigated radionuclide angiograms were obtained in the supine position. Changes in left ventricular chamber size from rest to exercise were calculated by comparing end-diastolic, end-systolic and stroke count rates. After PTCA, no patient had ≥50% luminal diameter narrowing or exercise-induced residual ischemia (Table I).

Before PTCA, the R-wave amplitude increased from rest to exercise in 2 patients, decreased in 2 patients and was unchanged (increase or decrease <0.5 mm) in 5 patients (Table II). After PTCA, at a heart rate approximating the pre-PTCA maximum, the change in R-wave amplitude increased in 4 and was unchanged in 5 patients. At the new peak exercise level, the R-wave amplitude increased from rest to exercise in 4 patients, declined in 3 patients and was unchanged in 2 patients. The mean R-wave amplitude change with peak exercise after PTCA was unchanged from both the pre-PTCA value and the post-PTCA submaximal exercise level.

Analysis of radionuclide end-diastolic count rates demonstrated that end-diastolic volume increased during supine exercise from 5 to 55% (mean ± standard deviation 26 ± 16%) relative to the resting volume before PTCA (Table II). After PTCA, the end-diastolic volume still increased during exercise (7 ± 10%), however, this increase was significantly less than that observed before PTCA ($p < 0.01$). End-systolic volume increased by more than 50% (57 ± 32%) during exercise in the pre-PTCA study. After PTCA, the relative end-systolic volume decreased by 14% (±17%) ($p = 0.0002$). No correlation was observed between changes in R-wave amplitude during exercise and changes in end-diastolic volume, end-systolic volume or stroke volume.

Theories to explain R-wave amplitude changes during exercise include changes in myocardial contractility, QRS axis shifts, conduction abnormalities, geometric and positional changes, coronary artery spasm and changes in intracardiac blood volume, i.e., the Brody effect. According to the Brody hypothesis, the heart is conceptualized as an elliptical mass of blood surrounded

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TABLE I Changes in Anatomic and Functional Indexes of Ischemia Before and After PTCA

	Catheterization						Treadmill			
	Stenosis (%)		Gradient (mm Hg)		Nuclear LVEF (%) RT-EX		Time (m + s)		Peak HR	
Pt.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	95	30	60	25	65–55	67–73	7m 18s	20m 42s	100	165
2	85	25	60	40	51–36	47–59	13m 04s	25m 30s	160	173
3	85	21	93	25	52–47	59–66	16m 55s	25m 15s	125	170
4	95	22	40	25	49–43	50–69	13m 25s	17m 30s	120	136
5	81	45	65	19	52–44	55–66	7m 47s	23m 17s	97	177
6	60	9	50	13	57–54	58–60	2m 25s	3m 55s	100	145
7	89	21	60	20	49–50	55–65	5m 05s	19m 15s	107	165
8	80	25	NR	15	65–43	58–61	3m 20s	15m 59s	75	128
9	74	35	53	38	61–43	57–68	5m 40s	16m 12s	95	130
Mean ± SD	83 ± 11	26 ± 10	60 ± 15	24 ± 9	56–46 ±7 ±6	56–65 ±6 ±5	8m20 ± 5m1s	18m37s ± 6m36s	109 ± 24	154 ± 20

HR = heart rate; LVEF = left ventricular ejection fraction; m + s = minutes and seconds; NR = not recorded; PTCA = percutaneous transluminal coronary angioplasty; RT-EX = rest-exercise; SD = standard deviation.

TABLE II Effects of PTCA on Exercise-Induced Changes in R-Wave Amplitude and LV Volume

	ΔR-ETT			%ΔEDCR		%ΔESCR	
		Post PTCA					
Pt.	Pre PTCA Rest-EX	Rest-EX2	Rest-EX	Pre PTCA Rest-EX	Post PTCA Rest-EX	Pre PTCA Rest-EX	Post PTCA Rest-EX
1	0	−0.2	−7.0	29	25	67	0
2	−2.1	0.2	−1.0	23	7	60	−19
3	−0.2	4.5	3.1	44	8	58	−11
4	0.4	1.8	2.3	14	−11	29	−45
5	−2.5	0.3	−4.2	56	3	82	−23
6	2.4	−0.2	−0.2	17	14	26	7
7	3.2	7.0	6.6	5	4	3	−20
8	−0.1	−0.6	0.1	15	14	85	5
9	−0.2	4.7	5.4	35	3	99	−23
Mean ± SD	0.1 ± 1.8	1.9 ± 2.8	0.6 ± 4.4	26.4 ± 16.2	7.4 ± 9.9	56.6 ± 31.5	−14.3 ± 16.5

ΔR-ETT = change in R-wave amplitude (mm) during exercise tolerance test; %ΔEDCR = % change end-diastolic count rates; %ΔESCR = % change end-systolic count rates; EX = peak exercise level determined before PTCA; EX2 = new peak exercise after PTCA; LV = left ventricular; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

by myocardium.[1] Because blood has a greater electrical conductivity than myocardial tissue, its presence and volume alter ("short circuit") the distribution of currents and, therefore, the body surface potentials measured electrocardiographically.

The normal response to upright exercise is a reduction in left ventricular volume due to exercise-induced tachycardia, catecholamine release and fluid loss. According to the Brody effect, a normal exercise response would be a decrease in the R-wave amplitude. Exercise-induced myocardial ischemia, if severe enough to cause left ventricular dilatation, should result in an increase in R-wave amplitude. In keeping with the Brody hypothesis, the R-wave amplitude has been shown to decrease during exercise in healthy people and stay the same or increase in patients with coronary artery disease.[2–4]

In this study, patients had exercise-induced ischemia before but not after PTCA. However, none demonstrated the predicted Brody response despite the normalization of exercise-induced left ventricular volume changes after successful PTCA. David et al[5] also failed to demonstrate a link between volume changes and R-wave amplitude. In their animal model, vena caval inflow obstruction after coronary ligation resulted in an increase in R-wave amplitude despite a rapid reduction in left ventricular end-diastolic volumes.

Some studies have demonstrated that patients with more extensive coronary artery disease are more likely to increase their R-wave amplitude during exercise.[6,7] This is consistent with the hypothesis that patients with more extensive coronary artery disease develop more profound ischemia and, therefore, are more likely to develop left ventricular dilatation. Although the patients in this study had only single-vessel coronary artery disease, all had multiple indexes for exercise-induced ischemia, including left ventricular dilatation before PTCA. These data are more consistent with the findings of Wagner et al,[8] who found no correlation between R-wave amplitude changes and the severity of coronary artery disease or left ventricular dysfunction.

Feldman et al[9] performed surface and intracoronary QRS measurements in 30 patients during the actual PTCA balloon inflation. In spite of the fact that all the patients demonstrated evidence for acute ischemia during the inflation, there was no coincident increase in R-wave amplitude. Wagner et al[10] also monitored their PTCA patients during balloon occlusion and concluded that the QRS changes were due in part to PR and ST baseline shifts. They hypothesized that "peri-ischemic block" (i.e., slowed intramyocardial conduction) was an important contributing factor.

In conclusion, we did not observe a correlation between exercise-induced R-wave amplitude changes and common indexes of ischemia, left ventricular function or chamber size. Therefore, we do not currently recommend that this measurement be used in routine diagnostic exercise studies.

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Percutaneous Transluminal Coronary Angioplasty in Octogenarians as an Effective Therapy for Angina Pectoris

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There are limited data regarding percutaneous transluminal coronary angioplasty (PTCA) in patients aged >80 years, a rapidly expanding population that has a 20% prevalence of symptomatic coronary artery disease.[1–3] Two studies have reported relatively low success rates, high procedural morbidity and mortality, and no data on restenosis,[4,5] whereas a third reported a higher success rate, but had limited angiographic follow-up—only in symptomatic patients.[6] We therefore undertook a study to assess the early and long-term outcome of octogenarian patients treated with PTCA.

From April 1986 to February 1990, 3,727 PTCA procedures, 2,783 of which were elective, were performed in the Interventional Cardiac Catheterization Laboratory at Duke University Medical Center. Patients were entered into a computerized medical information system that has been previously described.[7,8] Patients who underwent emergency PTCA in the setting of an acute myocardial infarction were not included in this study. Of this population, 31 patients (1%) >80 years old were identified. Patients with a successful procedure were considered eligible for the Duke PTCA restenosis follow-up protocol, involving repeat coronary angiography approximately 6 months after PTCA.[9]

Patients were brought to the Interventional Cardiac Catheterization Laboratory in the fasting state. Therapy with 325 mg/day of oral aspirin, 100 mg of oral dipyridamole administered 4 times daily, and calcium antagonists was begun the evening before unless specifically contraindicated. Patients were premedicated with diphenhydramine. After placement of femoral arterial and venous sheaths, patients were routinely given an intravenous heparin bolus of 10,000 to 12,000 U and 2,000 to 3,000 U/hour thereafter during the procedure. A temporary pacemaker was advanced to the confluence of the inferior vena cava and right atrium.

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Diagnostic coronary angiograms were recorded in orthogonal views through an 8Fr thin-wall guiding catheter of appropriate configuration. Coronary luminal diameter narrowing was graded on a previously described and validated ordinal scale (i.e., 0, <25, 25, 50, 75, 95 and 100%).[10,11] Angioplasty was performed with steerable, low-profile balloon catheter systems. Successful PTCA was defined as a reduction in coronary luminal diameter stenosis immediately after PTCA to ≤50% of the luminal diameter, as determined by visual inspection. Patients were typically maintained on heparin at 1,000 U/hour for 24 hours (partial thromboplastin time, twice the control) after angioplasty. Successfully dilated patients were discharged while receiving 325 mg of oral aspirin 4 times daily and a calcium antagonist, which they continued to receive through follow-up.

Thirty-one patients aged >80 years (median 82, range 80 to 86) underwent attempted PTCA on an elective basis between April 1986 and February 1990. Their clinical characteristics are listed in Table I. Most patients presented with progressive angina or unstable angina (55%). Sixty-one percent had 2- or 3-vessel disease. Median left ventricular ejection fraction was 55%. Thirteen patients (42%) had multilesion angioplasty. A total of 47 lesions were attempted in this cohort—26 in the left anterior descending coronary artery, 11 in the right coronary artery, and 10 in the left circumflex artery.

Outcomes of patients treated with PTCA are depicted in Figure 1. Angiographic success, defined as reduction to ≤50% residual stenosis of ≥1 coronary lesion, was achieved in 28 patients (90%, 95% confidence interval 80 to 100%). Overall, 43 of 47 lesions (91%) were successfully dilated—23 of 26 left anterior descending artery lesions (88%), 10 of 11 right coronary artery lesions (91%) and 10 of 10 left circumflex artery lesions (100%). The degree of stenosis was reduced from mean ± standard deviation 88 ± 9% before to 21 ± 17% after PTCA.

Three patients (10%) had unsuccessful attempts at PTCA and were referred for emergency coronary artery bypass grafting. Of this group, 2 developed dissections at left anterior descending PTCA sites despite multiple dilatations. They both underwent successful coronary artery bypass grafting and had an uneventful postoperative course. The third patient had a right coronary artery lesion that occluded after passage of a balloon catheter through the lesion; after bypass grafting, the patient died in the early postoperative period.

Three of the 28 patients with initially successful PTCA had repeat angiography while in the hospital for recurrent chest pain. Two patients (7%) who had typical angina pectoris had acute vessel closure. One of these had successful repeat PTCA of an optional diagonal vessel and did well subsequently. The second patient underwent repeat left circumflex artery dilatation but was left with poor distal flow and died several hours later from myocardial infarction. The third had a 50% stenosis at the PTCA site without impairment to coronary flow; no further intervention was performed and the patient did well thereafter. One other patient had an uncomplicated myocardial infarction due to embolic side-branch occlusion during a right coronary artery angioplasty. Of the 31 patients in this study, 29 (94%) were discharged in

TABLE I Clinical Characteristics of Percutaneous Transluminal Coronary Angioplasty Cohort (31 patients)

Median age (interquartile range)	82 (81,84)
Male (%)	13 (42)
Clinical features (%)	
Prior MI*	21 (68)
Cerebrovascular disease	5 (16)
Peripheral vascular disease	4 (13)
Diabetes mellitus	6 (19)
Hyperlipidemia	8 (26)
Diagnostic category (%)	
Asymptomatic post-MI	7 (23)
Stable angina	6 (19)
Progressive angina	8 (26)
Unstable angina/no IVNTG	6 (19)
Unstable angina/IVNTG	3 (10)
Palliation	1 (3)
Ejection fraction (%) (interquartile range)	55 (48,62)
Extent of coronary disease (%)	
1-vessel	12 (39)
2-vessel	16 (51)
3-vessel	3 (10)
Lesions successfully dilated (%)	43/47 (91)
Left anterior descending (%)	23/26 (88)
Left circumflex (%)	10/10 (100)
Right coronary (%)	10/11 (91)
Pre-PTCA stenosis (%)	88 ± 9
Post-PTCA stenosis (%)	21 ± 17

IVNTG = intravenous nitroglycerin; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

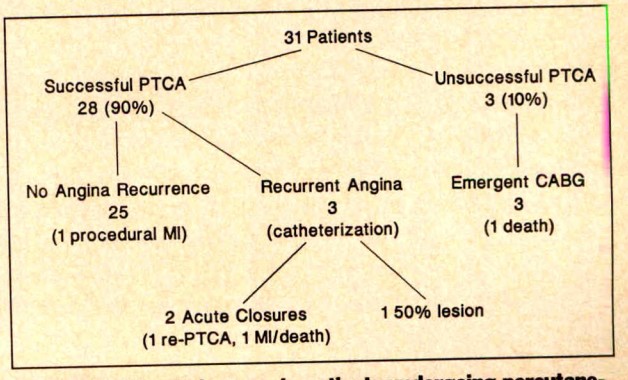


FIGURE 1. Hospital course in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). CABG = coronary artery bypass grafting; MI = myocardial infarction.

good condition from the hospital. The median hospital stay for all patients who underwent PTCA was 4 days (interquartile range 3 to 7).

Long-term clinical follow-up was obtained for all patients by telephone conversation with the patient, the patient's physician or family members, or both, as well as through the Duke Databank for Cardiovascular Diseases. Specifically, patients were queried regarding functional status, recurrence of angina, intercurrent hospitalization, myocardial infarction, and subsequent angioplasty or coronary artery bypass grafting. The mean (± standard deviation) duration of follow-up was 16 ± 11 months. Of the 27 patients discharged after successful PTCA, 22 (81%) were asymptomatic, remaining free of angina at follow-up. Five patients (20%) reported recurrent angina: 1 subsequently underwent repeat PTCA and another had a myocardial infarction. No patient underwent coronary artery bypass grafting after the time of discharge. There was 1 death during the follow-up period. The patient who required repeat PTCA 2 months after the initial encounter subsequently had a myocardial infarction while being hospitalized for acute pyelonephritis 1 month thereafter. For all 31 patients who initially underwent PTCA, the 1-year cumulative survival rate was 90% and the 1-year event-free survival rate (without myocardial infarction, coronary artery bypass grafting or death) was 84%.

All patients with successful procedures who had no medical contraindications or intervening events were requested to undergo repeat coronary angiography 6 months after angioplasty as part of an ongoing research protocol. Follow-up angiography was performed in multiple right anterior oblique and left anterior oblique projections to determine whether restenosis had occurred. Angiographic restenosis was defined as the presence of a >50% luminal diameter narrowing at the PTCA site.[11] When angioplasty was performed on >1 lesion (total 13 patients, 8 with angiographic follow-up), restenosis was defined as recurrence of a >50% luminal narrowing in any previously dilated lesion. Angiographic follow-up was obtained in 16 of the 26 patients (62%) eligible for study at a median of 6 months after PTCA. Ten patients who were eligible for repeat cardiac catheterization at 6 months did not undergo the procedure because of refusal on the part of the patient or the referring physician. Among the 16 patients who had angiography, 12 were asymptomatic and 4 had developed recurrent angina. Restenosis was observed in 5 of 16 patients (31%, 95% confidence interval 13 to 56%), 3 of whom were asymptomatic. In terms of lesions dilated, restenosis was detected in 6 of 26 lesions (23%, 95% confidence interval 8 to 38%).

The 3 previous reports regarding PTCA in patients >80 years old cite widely divergent success rates and no routine angiographic follow-up. Kern et al[4] reported a procedural success rate for PTCA in octogenarians of only 68%, with myocardial infarction or emergency bypass grafting occurring in 38%, and procedural death in 19%. Rizo-Patron et al[5] reported an angiographic success rate of 83% in octogenarians undergoing PTCA for unstable coronary syndromes. Complications still occurred in a significant proportion of patients—myocardial infarction in 5.5%, bypass grafting in 7.5% and death in 1.8%. Of 40 patients followed for a mean of 14 months, 87% had clinical improvement and event-free survival in the first year; 14 patients had repeat PTCA, 4 had bypass grafting and 4 died during follow-up. Jeroudi et al[6] reported a higher angiographic success rate of 93% with a low complication rate—myocardial infarction in 3.7% and death in 3.7%. Procedural success improved from before 1986 (75%) to after 1986 (95%). Fifty-two patients followed for a mean of 19 months had a 1-year 87% cumulative survival rate and an 81% event-free survival rate; 7 patients had ≥1 repeat angioplasty procedure, 4 had bypass grafting and 7 died. Angiographic follow-up in 19 symptomatic patients (37%) revealed restenosis in 11. The rate of restenosis could not be determined because only symptomatic patients underwent cardiac catheterization; restenosis was documented in 21% of the cohort and in 58% of patients who underwent repeat angiography.

PTCA is an effective means of revascularization in selected patients >80 years of age. Angiographic success was achieved in 90% of patients treated with PTCA and conferred sustained symptomatic relief in 81% of those successfully dilated. The overall 1-year cumulative survival rate of 90% and event-free survival rate of 84% further substantiates the favorable long-term outcome after PTCA. Because routine 6-month repeat angiography was sought in all patients and achieved in 62%, this study is the first to provide data that the restenosis rate (31%) in octogenarian patients is similar to that of younger cohorts.[12] PTCA should be considered an effective form of therapy for selected octogenarian patients with limiting coronary artery disease refractory to medical therapy.

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Feasibility of Out-of-Hospital Treatment of Supraventricular Tachycardias

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Despite the overall good prognosis, most patients with supraventricular tachyarrhythmias require hospitalization for the restoration of sinus rhythm. In the last decade, Mobile Coronary Care Units (MCCU) were instituted in several towns for the treatment of out-of-hospital cardiac arrest and to decrease prehospital times in acute myocardial infarction.[1] Cardiologist-staffed MCCUs can successfully attempt at-home cardioversion in patients with supraventricular arrhythmias, thus decreasing the number and cost of most hospitalizations.

The present study reviews the results of 10 years of activity by Florence's MCCU in the out-of-hospital treatment of recent onset (<24 hours) supraventricular tachyarrhythmias.

An MCCU has existed in Florence since 1979 and is now one of the mobile intensive care units of the Florence Prehospital System.[2] It operates 24 hours/day in the whole territory of the city (102.4 km²), which had, on January 1, 1990, 450,000 inhabitants. The ambulance, staffed with a cardiologist and 3 paramedics, is equipped with a portable monitor defibrillator, an electrocardiograph, an automatic ventilator and other equipment for advanced cardiac life support. In the period under study, the MCCU was activated either directly by citizens or by an operative center in the case of loss of consciousness, chest pain suspected to be symptomatic of coronary artery disease, and arrhythmias.

Florence's MCCU performed 8,789 interventions for out-of-hospital cardiac emergencies from November 25, 1979, to December 31, 1989. In 1,859 patients (21.1%), a supraventricular tachyarrhythmia was found. All patients underwent a careful physical examination and a 12-lead electrocardiogram was recorded. Diagnosis of the different types of arrhythmias was made according to standard electrocardiographic criteria.[3]

Medical history was obtained with particular attention paid to previous arrhythmic episodes, angina or old myocardial infarction, arterial hypertension, valvular heart disease, primary cardiomyopathies or preexcitation syndrome. Excluded from the study were patients with severe hemodynamic impairment, who were treated with direct-current shock, and patients with known sick sinus syndrome.

TABLE I Results of At-Home Treatment of Supraventricular Arrhythmias

	Atrial Fibrillation	Paroxysmal Supraventricular Tachycardia	Atrial Flutter	Other Atrial Arrhythmias
Total pts.	809	376	36	18
Converted to sinus rhythm	304 (37.6%)	311 (82.7%)	9 (25.0%)	7 (38.9%)
Not converted to sinus rhythm	419 (51.8%)	59 (15.7%)	26 (72.3%)	9 (50.0%)
Unknown	86 (10.1%)	6 (1.6%)	1 (2.7%)	2 (11.1%)
Hospitalized	280 (34.6%)	79 (21.0%)	21 (58.4%)	8 (36.2%)
Left at home	476 (58.8%)	285 (75.8%)	13 (36.2%)	8 (44.5%)
Refused hospitalization	53 (6.6%)	12 (3.2%)	2 (5.4%)	2 (11.0%)

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TABLE II Characteristics of Cardioverted and Noncardioverted Groups in the Different Arrhythmias

	Atrial Fibrillation		PSVT		Atrial Flutter		Other Arrhythmias	
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
Age (yrs)								
Males	63 ± 12	64 ± 12	57 ± 17	63 ± 13	76 ± 5	69 ± 6	69 ± 12	63 ± 8
Females	69 ± 13	71 ± 10	58 ± 16	58 ± 15	68 ± 17	73 ± 9	—	—
Heart rate (beats/min)	138 ± 26	135 ± 41	172 ± 30	167 ± 37	163 ± 29	147 ± 30	115 ± 39	109 ± 27
Prevalence of organic heart disease	217/304 (71%)	292/419 (70%)	270/300 (76%)	50/56 (87%)	5/9 (55%)	21/26 (81%)	5/7 (71%)	9/9 (100%)

(+) = patients restored to sinus rhythm; (−) = patients in whom the arrhythmia was not terminated.
PSVT = paroxysmal supraventricular tachycardia.

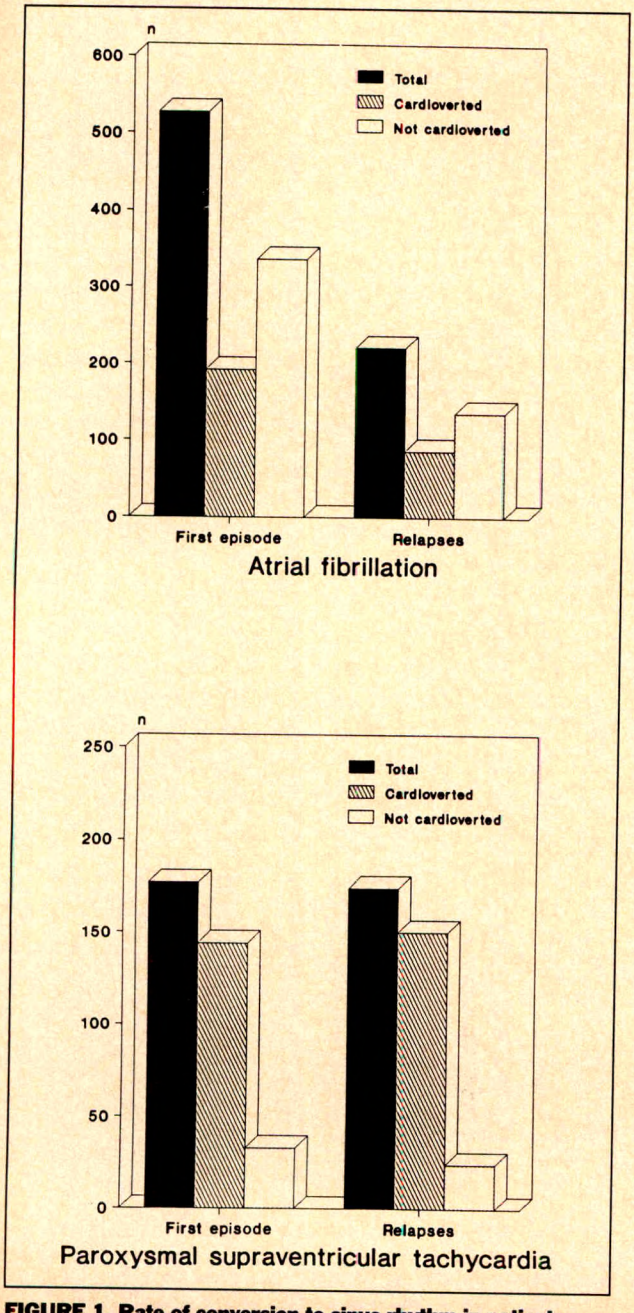


FIGURE 1. Rate of conversion to sinus rhythm in patients with first-onset or recurrent atrial fibrillation *(top)* and paroxysmal supraventricular tachycardia *(bottom)*.

In patients with paroxysmal (reentry) supraventricular tachycardia, vagal maneuvers were always attempted before drug administration. Pharmacologic treatment, given under continuous electrocardiographic monitoring and with frequent checks of arterial pressure, involved 1 of the following drugs: amiodarone, bunaftine, digoxin, propafenone or verapamil. The drug was administered via an intravenous route at frequently used therapeutic dosages.[4] If restoration of sinus rhythm did not occur within 30 minutes, a second drug could be tried. Patients whose sinus rhythm was restored and whose state did not raise particular diagnostic or therapeutic concerns after an additional hour of clinical observation were left at home, whereas patients whose arrhythmias persisted were usually hospitalized.

The present study population comprises 1,239 of the 1,859 patients with supraventricular arrhythmias rescued by our MCCU. Three-hundred twenty patients were excluded because the arrhythmia (mainly atrial fibrillation) lasted >24 hours, 38 because they fulfilled the exclusion criteria and 262 because data collection was largely incomplete.

Electrocardiographic diagnosis was atrial fibrillation in 809 patients (65.3%), reentry paroxysmal supraventricular tachycardia in 376 (30.3%) and atrial flutter in 36 (2.9%). In the remaining 18 patients, another atrial tachyarrhythmia was diagnosed.

At-home restoration of sinus rhythm was achieved in 631 of the 1,239 patients (51%). Seven-hundred eighty-two patients were left at home after MCCU intervention, whereas 388 were hospitalized. Hospitalization was refused by 69 patients (Table I).

Cardioversion was successful in 304 of 809 patients with atrial fibrillation. In patients whose arrhythmia was not terminated, heart rate significantly decreased (from 135 ± 52 to 109 ± 73 beats/min, $p < 0.001$). The cardioversion rate was slightly higher in patients with recurrences of arrhythmia than in patients with first-onset atrial fibrillation (Figure 1). Cardioverted and noncardioverted groups did not dif-

fer in age, sex distribution and prevalence of organic cardiopathies (Table II, Figure 2). Restoration of sinus rhythm was, however, significantly less frequent (23%) when the arrhythmia was associated with an acute cardiovascular event (Table III). Bunaftine and propafenone administration yielded the higher success rate (70 and 52%, respectively), whereas cardioversion was rare with amiodarone, digoxin and verapamil (Table IV).

Paroxysmal supraventricular tachycardia was terminated at home in 83% of patients. In the 59 patients in whom the arrhythmia persisted, heart rate decreased from 168 ± 38 to 139 ± 33 beats/min ($p < 0.002$). The success rate was higher in male patients of the younger age groups, but this did not apply to women (Table II). No difference in cardioversion rates was found between patients with first-onset paroxysmal supraventricular tachycardia and those with previous arrhythmic episodes. Arrhythmia was less frequently terminated in patients who had an associated acute cardiovascular event; however, the difference did not reach statistical significance. Vagal maneuvers were successful in 23 patients (6.1%); among the drugs used, verapamil had the higher success rate (Table IV).

In only 25% of patients with atrial flutter was sinus rhythm restored. No significant slowing of ventricular rate was achieved in noncardioverted patients. Success rate was not affected by sex, age or the drug used.

Restoration of cardiac rhythm was achieved in 7 of 18 patients (38.9%) with different atrial tachyarrhythmias. This group is too small for statistical analysis; however, the pattern of success was similar to that of patients with atrial fibrillation.

No major adverse effects were observed in our patients: mild hypotension occurred in 14 patients (10 with verapamil), while a proarrhythmic effect (appearance or increase in number or complexity of ventricular premature beats) was demonstrated in 15 (7 with bunaftine) (Table V). One patient had sinus standstill lasting 6 seconds that was associated with transient hypotension during propafenone.

The present results indicate that at-home treatment of recent onset supraventricular arrhythmias can be accomplished by cardiologist-staffed MCCUs without significant risks, allowing a 50% decrease in immediate hospitalization. The lower percentage of atrial fibrillation converted to sinus rhythm in the present study, compared with others,[5,6] may require different explanations. First, as the times of MCCU intervention are necessarily brief (mean 1 hour), many late conversions may occur in hospitalized patients and thus escape our observation.[3] Second, previous investigations demonstrated that, in a substantial number of patients, sinus rhythm restoration

TABLE III Results of Treatment in Patients with Associated Acute Cardiovascular Events

	Atrial Fibrillation	Paroxysmal Supraventricular Tachycardia
Angina	20/72	7/9
Myocardial infarction	4/22	2/5
Pulmonary edema	7/38	7/10

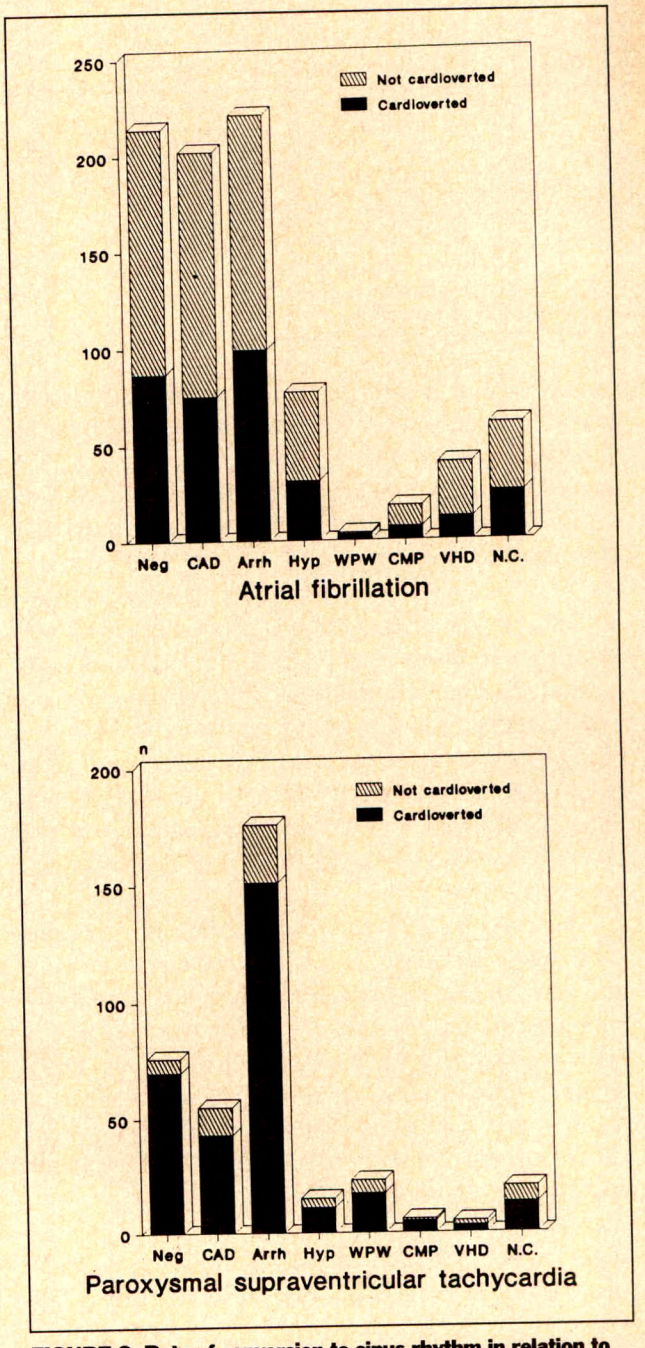


FIGURE 2. Rate of conversion to sinus rhythm in relation to cardiac precursors in atrial fibrillation *(top)* and paroxysmal supraventricular tachycardia *(bottom)*. Arrh = previous arrhythmic episodes; CAD = coronary artery disease; CMP = primary cardiomyopathies; Hyp = arterial hypertension; N.C. = data not collected; Neg = negative; VHD = valvular heart disease; WPW = Wolff-Parkinson-White syndrome.

TABLE IV Cardioversion Rate with Single-Drug Administration in the Different Types of Supraventricular Arrhythmias

	Atrial Fibrillation	PSVT	Atrial Flutter	Other
Amiodarone	5/38	5/7	0/1	0/1
Bunaftine	75/107	32/37	2/4	1/2
Digoxin	17/81	4/6	1/4	—
Propafenone	124/239	62/77	1/3	2/2
Verapamil	8/48	119/138	2/6	2/2

Abbreviation as in Table II.

TABLE V Side Effects of Pharmacologic Treatment

	No. of Patients Treated	Hypotension	Arrhythmias	Neurologic Side Effects	Other
Amiodarone	47	0	1	0	0
Bunaftine	150	2	5	1	6
Digoxin	95	0	0	0	2
Propafenone	321	2	4	0	0
Verapamil	194	8	3	0	1
Bunaftine + verapamil	58	2	2	1	1
Propafenone + verapamil	29	0	0	1	1

was possible only with oral quinidine or direct-current shock,[6,7] treatment not suitable for an out-of-hospital emergency system. The cardioversion rate with class IA and IC antiarrhythmic drugs ranged from 35 to 76%,[8,9] a figure similar to that observed in the present study with bunaftine or propafenone.

At variance with previous reports,[10] the cardioversion rate was not significantly different between patients with organic heart disease and patients with lone atrial fibrillation. However, restoration of sinus rhythm was less frequent when the arrhythmia was associated with an acute cardiovascular event. Hemodynamic abnormalities or myocardial ischemia, or both, in our patients may have acted as additional pathophysiologic factors and may account for the lower efficacy of antiarrhythmic treatment.

Restoration of sinus rhythm was much more commonplace in patients with paroxysmal supraventricular tachycardia. Our results confirm that vagal stimulation must be tried in every patient with paroxysmal supraventricular tachycardia before drug administration. Drug-induced cardioversion occurred in percentages similar to those in previous published reports.[11,12] No significant differences were found among the drugs used, even if the success rate was slightly higher for verapamil.

Sinus rhythm restoration was achieved in only 9 patients with atrial flutter, and this confirms the resistance of atrial flutter to pharmacologic treatment. Direct-current shock and overdrive suppression remain the methods of choice for restoration of sinus rhythm in patients with this arrhythmia.

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Short-Term Efficacy and Safety of a Single Five-Milligram Dose of Oral Nifedipine in Uncontrolled Essential Systemic Hypertension

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Nifedipine has been extensively and successfully used for the treatment of various hypertensive syndromes in doses of ≥10 mg[1]; such doses have a harmful potential, at least in the elderly.[1-8] As there are only scant reports about the use of smaller doses of nifedipine,[9,10] we undertook this clinical study to test the effectiveness and safety of a single 5-mg dose of oral nifedipine in patients admitted to our Emergency Care Department with uncontrolled moderate to severe hypertension.

Only patients with essential hypertension were treated if the diagnosis had been present for ≥1 year and, if previously normotensive under medical treatment, they had a gradual elevation of the diastolic blood pressure (BP) to values from 110 to 129 mm Hg. Excluded were patients with coexisting valvular heart disease or acute myocardial infarction, those who were pregnant or who were receiving calcium antagonists within the previous 12 hours, or those with hypertensive urgencies and emergencies.

Fifty-two consecutive patients (33 women and 19 men aged 31 to 70 years [mean ± standard deviation 51 ± 11]) fullfilling the aforesaid criteria were treated. All underwent clinical history, physical examination, fundoscopy, electrocardiography at rest, chest roentgenography, and basic blood chemistry sampling. A monitor for continuous electrocardiographic display and intravenous 5% glucose in water were installed for safety reasons.

Patients were divided into 2 groups: group A, diastolic BP from 110 to 119 mm Hg, and group B, diastolic BP from 120 to 129 mm Hg; 6 patients in group A and 7 in group B had signs of hypertensive heart disease on chest x-ray and on electrocardiography. In an open trial, all patients received a single 5-mg dose of nifedipine by chewing a multipierced capsule. Heart rate and supine BP were recorded immediately before and 5, 15, 30, 45 and 60 minutes after drug ingestion and then every 30 minutes until minute 180. The same observers monitored all BP and heart rate recordings; phase I and V of the Korotkoff sounds were considered systolic and diastolic BP.

BP and heart rate changes were registered and compared with pretreatment values using Student's t test; differences at the $p < 0.01$ level were considered statistically significant. Values for BP (mm Hg) and heart rate (beats/min) are given as mean ± 1 standard deviation. The criterion for efficacy was the achievement of a diastolic BP of ≤100 mm Hg within the observation period.

Forty-seven patients had statistically significant changes in systolic and diastolic BP; 3 patients in group A and 2 in group B did not, even after receiving another 5-mg dose of nifedipine 30 to 45 minutes later. Changes in diastolic BP became statistically significant at minute 5 and remained significant during the total observation period in both groups ($p < 0.001$) (Figure 1).

Mean values of pre- and post-treatment systolic and diastolic BP at peak effect for group A were from 160 ± 5/111 ± 3 to 150 ± 8/95 ± 8 mm Hg; for group B, mean values were from 171 ± 10/121 ± 2 to 154 ± 12/98 ± 11 mm Hg. Results were also analyzed according to age: for 38 patients ≤60 years old, mean initial and post-treatment values at peak effect were 167 ± 10/118 ± 5 and 153 ± 10/96 ± 11 mm Hg, respectively ($p < 0.001$); for 14 patients >60 years old, mean values were 170 ± 10/119 ± 5 and 151 ± 9/93 ± 10 mm Hg, respectively ($p < 0.001$). The mean values of initial and post-treatment heart rate at peak effect in group A ranged from 73 ± 10 to 76 ± 12 beats/min (difference not significant); in group B, mean values ranged from 81 ± 12 to 85 ± 12 beats/min (difference not significant).

After 180 minutes of observation, all patients were discharged to their attending physicians; oral medications for long-term control were begun immediately before discharge. No patient developed a diastolic BP ≤80 mm Hg, angina, electrocardiographic signs of myocardial ischemia, or neurologic dysfunction; 3 patients complained of mild headache and 3 others had palpitations.

Doses of 10 to 20 mg of sublingual or oral nifedipine are used extensively for the management of uncontrolled systemic hypertension, hypertensive crises and emergencies, and various forms of ischemic heart disease with

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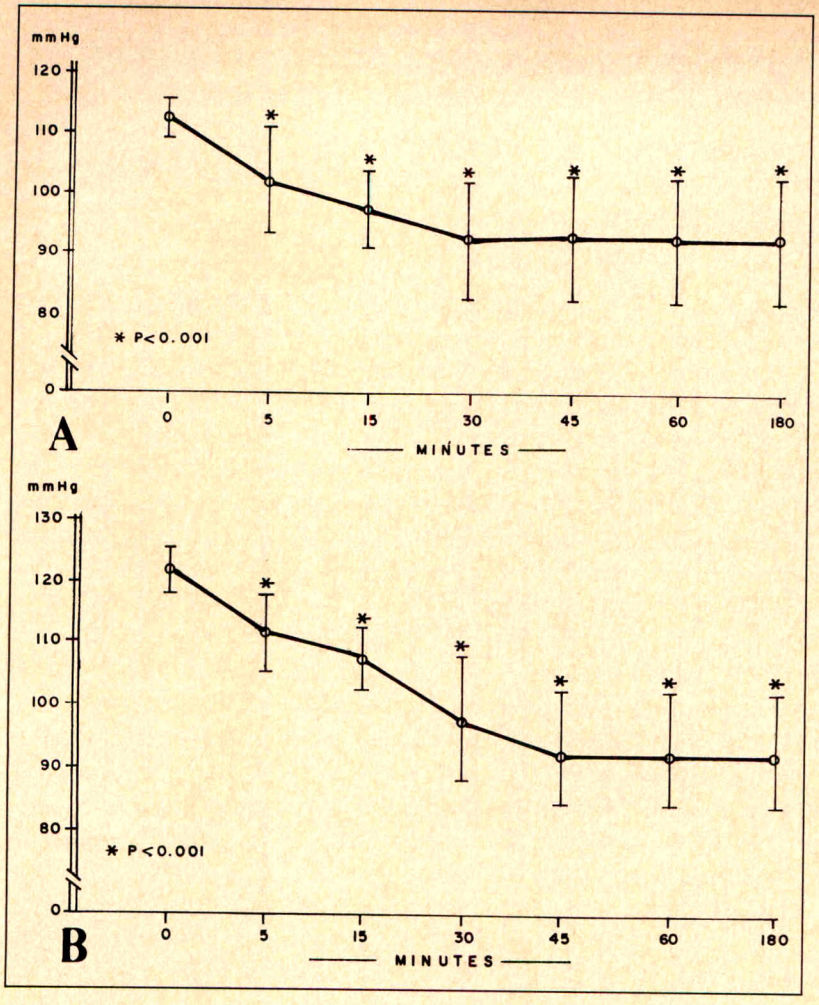


FIGURE 1. Diastolic blood pressure response after a single 5-mg dose of nifedipine. Reductions in diastolic blood pressure became statistically significant at minute 5 in *(A)* 21 patients with a diastolic blood pressure of 110 to 129 mm Hg and in *(B)* 31 patients with a diastolic blood pressure of 120 to 129 mm Hg.

or without left ventricular failure with excellent results.[1,11–13] The adverse effects of such doses have been minimal and without consequences in several hundred patients,[1,12] but mishaps have been described,[2–8] apparently related to vasodilation and decrease in flow to vital organs; the adverse effects were described in patients >50 years old, usually within 60 to 90 minutes of receiving the drug, except in the case of renal dysfunction. For this reason we decided to test the immediate efficacy and safety of a 5-mg dose of nifedipine by the oral route in patients with uncontrolled moderate to severe essential hypertension, 1 of the leading causes of admission to our Emergency Care Department. The 5-mg dose induced a highly statistically significant reduction of BP in both groups, starting at minute 5 and lasting for the total period of observation; the results were equally satisfactory in patients ≤ and >60 years old. The 5-mg dose was not effective in 5 patients, and no response was seen when it was repeated; this also has been reported with larger doses.[10]

No patient showed signs of decreased perfusion to vital organs. Adverse effects, palpitations and headache, were mild and transitory. Heart rate changes were neither clinically nor statistically significant.

Even if our results pertain only to the short-term effects in patients with uncontrolled moderate to severe essential hypertension, we believe that the use of the 5-mg dose of oral nifedipine, alone or in conjunction with other drugs, could be extended to other hypertensive syndromes—for example, hypertensive urgencies and emergencies, aortic dissection, elderly patients with systolic and diastolic hypertension with past medical histories of ischemic brain disease or those under treatment with other drugs. Further studies could show if this reduced dose is as effective in such circumstances as it was in our patients. The 5-mg dose is also attractive because it can be repeated if necessary, without the potential danger represented by repeating larger doses of the drug.

In conclusion, the efficacy and safety of a single 5-mg dose of oral nifedipine was tested and confirmed in a group of patients with uncontrolled moderate to severe essential hypertension. The dose induced statistically significant reductions of the elevated BP and no untoward effects in patients with a diastolic BP of 110 to 129 mm Hg.

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Detection of Patent Foramen Ovale by Doppler Color Flow Mapping in Patients Undergoing Cardiac Catheterization

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Autopsy studies have demonstrated that the foramen ovale is patent in 20 to 35% of the general population.[1,2] Although it is generally considered to be an incidental finding, recent clinical studies suggest that the patent foramen ovale (PFO) may serve as an important route for paradoxical embolization.[3,4] In addition, hypoxemia due to right-to-left shunting across a PFO may occur in the setting of elevated right heart pressures or decreased right ventricular compliance.[5,6] Although contrast echocardiography has been used to identify right-to-left shunting in patients with a suspected PFO,[4,7–10] this technique may be limited by its dependence on a right-to-left component of flow and by the small number of cardiac cycles in which to identify such flow. Doppler color flow mapping, which can image flow jets in either direction across an atrial septal defect,[11] also offers the potential to identify flow across a PFO. Thus, we tested the hypothesis that color flow mapping could accurately detect small jets resulting from flow across a PFO.

We studied 34 patients (Table I) by transthoracic Doppler color flow mapping, 6 of whom also underwent transesophageal echocardiography (TEE) to evaluate PFO. All patients underwent diagnostic cardiac catheterization for the evaluation of coronary artery disease (n = 17), valvular heart disease (n = 7), coronary angioplasty (n = 5) or dilated cardiomyopathy (n = 2). An additional 7 patients were entered into the study but were excluded due to technically inadequate echocardiograms.

After informed consent, right-sided cardiac catheterization was performed using a 7Fr or 8Fr woven Dacron™ catheter. A PFO was considered present if the catheter crossed the interatrial septum into the left atrium, and if its position was confirmed oximetrically (oxygen saturation ≥90%) and hemodynamically (left atrial pressure wave form). By these criteria, a PFO was present in 10 patients. None had oximetric evidence of left-to-right shunting by the criteria of Dexter et al.[12] In 2 patients, left-to-right shunting was excluded by hydrogen inhalation.[13] The 24 patients in whom the catheter did not cross the interatrial septum served as control subjects. Although color flow imaging was generally performed after catheterization, PFO was detected before catheterization in 3 patients. In these 3, repeat color flow mapping after catheterization revealed no change in the pattern of flow across the PFO. Thus, we do not believe that crossing a PFO at catheterization subsequently influenced color flow images of flow across the PFO.

Transthoracic color flow imaging was performed with a Vingmed CFM 700, a Hewlett-Packard Sonos 500 or a Hewlett-Packard Sonos 1000. The interatrial septum was carefully interrogated in the parasternal short-axis, apical 4-chamber and subcostal views in each patient to obtain optimal visualization of the fossa ovalis. Doppler color flow mapping was performed with a conventional velocity-variance map. The color gain was adjusted to the setting just below

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TABLE I Clinical and Hemodynamic Characteristics

Pt. No.	Age (yr) & Sex	Diagnosis	Oxygen Saturation (%)			Pressure (mm Hg)		Color Flow Jet Direction	
			SVC	RA	LA	LA	RA	Rest	Maneuvers
Patients with Patent Foramen Ovale									
1	61M	AS	64	63	95	11	4	L → R	R → L
2	70M	MR	65	67	92	11	6	L → R	—
3	18F	DC	72	74	92	24	7	L → R	No reversal
4	65M	CAD	62	65	92	8	4	L → R	—
5	58F	CAD	68	71	95	8	4	L → R	R → L
6	41M	CAD	69	68	94	11	5	L → R	R → L
7	32F	CAD	80	80	93	8	5	L ↔ R	—
8	54F	CAD	79	78	95	2	1	L → R	No reversal
9	47M	CAD	69	73	96	—	—	L → R	R → L
10	65M	CAD	63	58	93	11	7	None	No reversal
Control Subjects									
11	58M	AR	61	59	—	—	6	0	—
12	62M	AS	66	69	—	—	3	0	0
13	56F	AS	68	69	—	—	6	0	0
14	63F	AS	64	60	—	—	3	0	0
15	60M	MR	41	47	—	—	8	R → L	0
16	33M	DC	49	57	—	—	11	0	0
17	62M	CAD	62	64	—	—	4	0	—
18	77M	CAD	64	66	—	—	4	0	—
19	53M	CAD	66	68	—	—	—	0	0
20	77M	CAD	65	63	—	—	—	0	—
21	60M	CAD	59	61	—	—	3	0	0
22	48M	CAD	66	74	—	—	—	0	0
23	54M	CAD	56	58	—	—	—	0	0
24	63M	CAD	52	52	—	—	—	L → R	0
25	70M	CAD	50	49	—	—	—	0	—
26	40M	CAD	72	76	—	—	—	0	0
27	70M	CAD	39	41	—	—	7	0	0
28	59M	CAD	68	69	—	—	—	0	0
29	44F	CAD	—	—	—	—	—	0	—
30	47M	CAD	—	—	—	—	—	0	0
31	64M	CAD	52	50	—	—	—	0	0
32	62M	CAD	83	83	—	—	5	0	0
33	64M	CAD	68	67	—	—	—	0	0
34	60F	CAD	73	71	—	—	10	0	0

AR = aortic regurgitation; AS = aortic stenosis; CAD = coronary artery disease; DC = dilated cardiomyopathy; LA = left atrium; L → R = left-to-right flow; L ↔ R = bidirectional flow; MR = mitral regurgitation; RA = right atrium; R → L = right-to-left flow; SVC = superior vena cava; — = no information available or not done; 0 = negative or absent.

that in which background noise appeared. Because flow across a PFO may occur only intermittently, we deemed it important to use the highest possible frame rate. Thus, depth and sector angle settings were adjusted to maximize frame rate while maintaining visualization of the fossa ovalis. Frame rates ranged from 10 to 21 frames/s and Nyquist velocities ranged from 49 to 80 cm/s. Color flow mapping of the interatrial septum was performed at rest in all patients, during a series of brief coughs in 21 subjects, and with the release of a Valsalva maneuver in 18.

TEE was performed using a 5-MHz transducer (Hewlett-Packard Sonos 1000) in 6 subjects after evaluation of coagulation status and exclusion of possible contraindications to esophageal intubation. Patients were sedated with a combination of 1 to 3 mg of intravenous midazolam and 25 to 50 mg of intravenous meperidine, and were monitored for heart rate, blood pressure and arterial oxygen saturation. TEE images were obtained to optimize visualization of the fossa ovalis and color flow maps were then generated.

All echocardiographic studies were reviewed separately in blinded fashion by 2 experienced echocardiographers, and a consensus was reached regarding the presence and direction of flow across the fossa ovalis. Specific criteria for diagnosis of flow across a PFO were (1) continuity of the flow jet with the region of the fossa ovalis, (2) color flow signals on both sides of the fossa ovalis, and (3) the presence of either velocity variance or a velocity gradient within the jet, wherein the central core of the jet contained higher velocities (represented by brighter hues) and the jet periphery contained lower velocities (represented by darker hues) (Figure 1).

The sensitivity, specificity and positive and negative predictive values of color flow mapping for the

detection of flow across a PFO were calculated in the group studied by transthoracic imaging. In the group studied by TEE, statistical analyses were not performed because the numbers (3 patients with PFO, 3 control subjects) were small.

Hemodynamic data and clinical diagnoses for the study group are listed in Table I. No patient with PFO had a history of paradoxical embolization. Flow jets across the fossa ovalis were seen in 9 of 10 patients with a documented PFO (sensitivity 90%) and in 2 of 24 control subjects (specificity 92%). Positive and negative predictive values for color flow mapping in detecting flow across a PFO were 82 and 96%, respectively. Of the 9 patients with PFO correctly identified by color flow studies, flow at rest was left to right in 8 and bidirectional in 1. Of the 2 control subjects with color flow studies meeting the criteria for a PFO, 1 had left-to-right flow at rest, and the other had right-to-left flow at rest. Either cough or Valsalva maneuver was performed in 7 of 10 patients with PFO and in 14 control subjects. Reversal of interatrial flow was seen in 4 patients with PFO; however, right-to-left flow was not provoked by maneuvers in any patient in whom left-to-right flow was not already present. The subcostal view provided the best results (Table II). In this view, flow was seen in 9 of 10 patients with a PFO and in 2 of 24 control subjects (sensitivity 90%, specificity 92%, positive predictive value 82%, negative predictive value 96%).

TABLE II Sensitivity, Specificity and Predictive Values of Doppler Color Flow Mapping in the Detection of Patent Foramen Ovale

	Echocardiographic View		
	Subcostal	Apical 4-Chamber	Short-Axis
Sensitivity (%)	90	70	0
Specificity (%)	92	92	96
Positive predictive value (%)	82	78	0
Negative predictive value (%)	96	88	70

TEE was performed in 3 patients with a PFO and in 3 control subjects. In each case, TEE provided excellent anatomic detail of the interatrial septum, clearly demonstrating a defect in the fossa ovalis in the patients with a PFO. Moreover, left-to-right flow across the fossa ovalis was clearly seen by TEE in all 3 patients with a PFO (Figure 2).

PFO occurs frequently in the normal population and is usually considered a normal variant.[1] Although left-to-right shunting (as measured oximetrically) does not usually occur across a PFO, the potential for right-to-left shunting or paradoxical embolization is well recognized. It has been suggested that patients with a PFO may be at increased risk for embolic stroke.[4] Thus, accurate, noninvasive diagnosis of PFO may be clinically important, particularly in otherwise healthy persons with unexplained stroke. This study demonstrates that Doppler

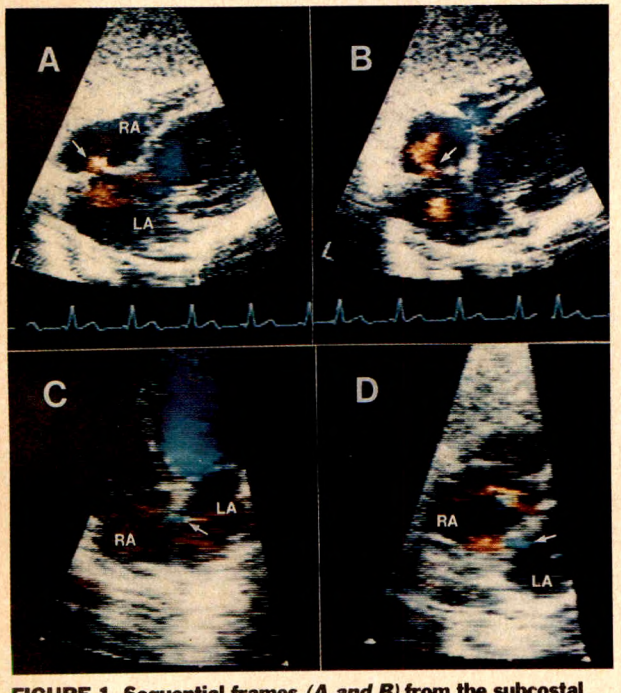


FIGURE 1. Sequential frames *(A and B)* from the subcostal view revealing left-to-right flow across a catheter-proved patent foramen ovale. The flow jet *(arrow)* is continuous with the fossaovalis and flow is seen on both sides of the interatrial septum. A velocity gradient is present from the central core *(yellow)* to the jet periphery *(dark red)*. Apical 4-chamber *(C)* and subcostal *(D)* views revealing right-to-left flow with cough in a different patient. A blue jet *(arrow)* is clearly seen on both sides of the fossa ovalis. LA = left atrium; RA = right atrium.

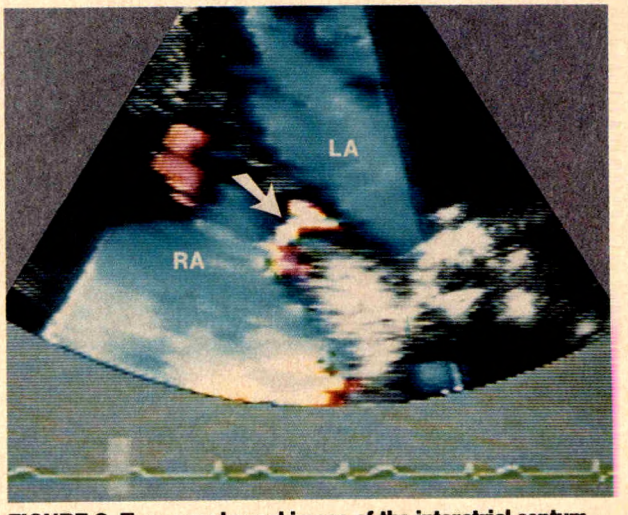


FIGURE 2. Transesophageal image of the interatrial septum in a patient with a patent foramen ovale. Left-to-right flow across the patent foramen ovale *(arrow)* is clearly seen with Doppler color flow imaging. The diagnosis of patent foramen ovale was subsequently confirmed at surgery (mitral valve replacement) in this patient. Abbreviations as in Figure 1.

color flow mapping is both sensitive and specific in detecting flow across a PFO. Moreover, these data establish that, contrary to traditional teaching, left-to-right flow across a PFO often occurs in patients undergoing catheterization.

Although the ability of 2-dimensional contrast echocardiography to detect right-to-left shunting across a *presumed* PFO is well established,[4,7–9] only 1 study[10] directly compared contrast echocardiography with catheterization. The present study, in which invasive data were obtained in all patients, demonstrates that color flow mapping is useful in detecting left-to-right flow in patients with a PFO, and that flow reversal with cough or Valsalva does not occur in all these patients. Although we did not directly compare contrast echocardiography with color flow mapping in this study, the 2 techniques may be complementary. Color flow mapping is a tomographic technique that, as shown in this study, can detect left-to-right flow across a PFO. However, movement of the imaging plane during cough or Valsalva maneuver may limit the ability of color flow mapping to detect right-to-left flow. Contrast echocardiography, which is less dependent on the imaging plane, may be superior in detecting right-to-left flow during provocative maneuvers.

Color flow jets across the fossa ovalis were considered to be present in 2 subjects in whom catheterization did not reveal a PFO. Potential reasons for false-positive color flow studies include (1) mitral or tricuspid regurgitant jets directed toward the interatrial septum and producing variance in the region of the fossa ovalis, (2) prominent inferior vena cava flow or pulmonary venous inflow along the interatrial septum, and (3) a PFO present but not detected at catheterization.

Interatrial flow across an atrial septal defect (as opposed to a PFO) is determined by the size of the defect, the relative compliance of the ventricles and the relative resistances of the pulmonary and systemic vascular circulations[14] because there is no pressure gradient between the 2 atria. In the setting of a PFO, the normal interatrial pressure gradient may more importantly influence the magnitude and direction of flow, as suggested by the finding of left-to-right flow jets by Doppler color flow mapping in this study. Doppler color flow imaging, which maps the spatial distribution of velocities, is capable of detecting extremely low flows driven across small orifices by small pressure gradients.[15] Thus, it is not surprising that color flow mapping was more sensitive than oximetry or hydrogen inhalation for detecting the very small amount of left-to-right flow that may occur across a PFO.

Right-to-left flow and paradoxical embolization must occur under conditions that result in reversal of the normal interatrial pressure gradient. Such a flow reversal would be expected to occur during cough or the release phase of Valsalva maneuver, and was seen in 4 of 7 patients in whom these maneuvers were performed. However, it must be emphasized that we predominantly studied patients with coronary artery disease, in whom alterations in left ventricular compliance may have attenuated the expected reversal of the interatrial pressure gradient during maneuvers, thus preventing the detection of right-to-left flow.

The optimal window for detecting flow across a PFO is the subcostal view, wherein the fossa ovalis is well delineated and the transducer is nearly parallel to flow across the septum. In addition, the origin of venous inflow from the inferior vena cava is clearly identified and differentiated from flow across the interatrial septum. In the patient for whom diagnosis of a PFO is critical, or in whom a technically adequate transthoracic study is not possible, TEE appears to be the procedure of choice. However, transthoracic color flow mapping is more widely available, is noninvasive, does not require the presence of a physician, does not have the risk of intravenous sedation and, as shown in this study, is accurate in detecting a PFO.

In conclusion, Doppler color flow mapping is accurate in detecting flow across a PFO in patients undergoing cardiac catheterization. TEE may be the procedure of choice for patients in whom a technically adequate transthoracic study cannot be obtained, or in whom the diagnosis of PFO is critical. Finally, contrary to traditional teaching, left-to-right flow across a PFO frequently occurs in this patient population.

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Exercise Hemodynamics and Oxygen Delivery Measurements Using Rebreathing Techniques in Heart Transplant Patients

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The cardiorespiratory response to graded exercise in cardiac transplant patients differs from that in normal subjects partly because denervated hearts are much less responsive to changes in autonomic nervous system input. Previous studies with transplant patients have shown a delayed and often diminished heart rate response to exercise compared with normal subjects.[1,2] Although it has been assumed that increases in stroke volume, using the Frank-Starling mechanism, compensate for the delayed heart rate response during exercise, little is known about the matching of cardiac output ($\dot{Q}_T$) to oxygen uptake ($\dot{V}O_2$) in cardiac transplant patients. During exercise the metabolic requirements of skeletal muscle, a function of the work load and the size of the active muscle mass, are the major determinants of $\dot{Q}_T$ and systemic O_2 transport.[3] The relation between $\dot{Q}_T$ and $\dot{V}O_2$ in normal subjects during exercise has been studied extensively and found to be relatively constant at 5 to 6 liters of blood flow, $\dot{Q}_T$, per liter of change in $\dot{V}O_2$ /min.[4–6] This is approximately a 1:1 ratio between exercise-induced increases in O_2 transport relative to levels at rest. Because the normal heart relies primarily on an increase in heart rate to increase $\dot{Q}_T$ during exercise, with only minimal change in stroke volume, it is reasonable to expect that the transplant patient will have a suboptimal response to exercise. This study was conducted to determine the characteristics of the cardiovascular response to upright bicycle exercise in cardiac transplant patients. In particular, the $\dot{Q}_T$ to $\dot{V}O_2$ relation during exercise in the transplant patients was compared with that of normal subjects to determine if $\dot{Q}_T$ was appropriately matched to $\dot{V}O_2$ during exercise.

The acetylene rebreathing system used to measure pulmonary capillary blood flow ($\dot{Q}_c$) and $\dot{V}O_2$ during exercise was developed in our laboratory.[7] Measurements of $\dot{Q}_c$ have been compared with simultaneously measured indicator dye dilution (CO_{ID}).[8,9] Triebwasser et al[19] showed excellent correlation (r = 0.94) between CO_{ID} and $\dot{Q}_c$ with a slope not different from identity, and Kally et al[8] showed a similar correlation (r = 0.97), and that $\dot{Q}_c$ insignificantly overestimates CO_{ID} by 2 ± 9% in normal lungs and that in patients with obstructive lung disease $\dot{Q}_c$ again insignificantly overestimates CO_{ID} by 6 ± 15%. Because of the high degree of accuracy and precision of $\dot{Q}_c$ with CO_{ID}, we made calculations such as stroke volume and cardiac index using $\dot{Q}_c$ as the value for $\dot{Q}_T$. Gas concentrations were measured with a Perkin-Elmer MGA-1100 mass spectrometer (Pomona, California) and calculations for $\dot{Q}_c$ were made according to the method described by Sackner et al.[10] Lung tissue volume value was estimated from a study of normal subjects.[11] Test gas composition was 0.79% acetylene, 9.18% helium, 39.00% O_2 and 60.03% nitrogen. Calibration was performed initially and after every other rebreathing measurement with the gravimetrically mixed test gas and room air. Room air values were assumed to be 20.94% O_2, 0.94% argon, 0.04% carbon dioxide and 78.08% nitrogen. The initial rebreathing test gas volume was 1,000 ml for men and 800 ml for women. Rebreathing gas volume was increased by 200

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TABLE I Hemodynamic Variables

Pt. No.	Age (yr) & Sex	Resting HR (beats/min)	Max. HR (beats/min)	ΔHR* (beats/min)	Max. $\dot{V}O_2$ (ml/kg/min)†	Max. $\dot{Q}_c$ (liter/min)	Max. CI (liter/min/m²)	Max. $C_{(a-v)O_2}$ (ml/100 ml blood)	Max. SV (ml)	Max. Exercise (watts)
Transplant Patients										
1	29M	70	90	20	18.0	14.1	6.3	12.5	156	125
2	26M	71	118	47	25.3	16.8	9.8	10.7	142	125
3	41M	90	104	14	12.2	10.7	5.2	10.3	103	75
4	47M	111	127	16	14.5	10.9	5.2	12.3	86	50
5	20M	99	126	27	17.1	12.1	6.0	11.3	96	100
6	21M	104	150	46	17.3	12.6	6.2	11.3	84	100
7	40M	125	151	26	20.2	9.5	4.9	15.3	63	100
8	24F	117	137	20	16.6	6.9	4.3	13.7	50	75
Mean SD	31 ± 10	98 ± 20	125 ± 21	27 ± 13	17.6 ± 3.9	11.7 ± 3.0	6.0 ± 1.7	12.2 ± 1.7	98 ± 36	94 ± 26
Normal Subjects										
1	47M	68	155	87	37.5	16.6	8.9	16.5	107	200
2	29M	70	181	111	40.4	24.0	11.6	13.7	133	250
3	28M	87	161	74	31.8	18.6	9.0	13.5	116	200
4	31M	65	162	77	41.4	22.2	11.2	13.8	137	250
5	28M	74	173	99	36.1	15.9	8.8	14.7	92	175
6	29M	77	133	56	22.3	16.9	7.9	13.0	127	150
7	27M	70	164	94	42.2	19.9	11.2	14.0	121	200
8	33F	84	174	90	28.6	13.1	8.3	11.8	75	125
9	35M	65	185	140	49.2	21.7	11.2	16.3	117	300
10	42M	106	170	64	27.8	12.8	7.6	12.9	75	125
11	38F	77	172	95	22.5	18.2	8.1	13.6	106	175
Mean SD	33 ± 7	76 ± 13	166 ± 14	90 ± 23	34.5 ± 8.6	18.2 ± 3.6	9.4 ± 1.5	14.0 ± 1.4	109 ± 21	195 ± 55

*ΔHR = change in heart rate from rest to maximal heart rate.
†Standard temperature and pressure, dry.
$C_{(a-v)O_2}$ = arterial-venous oxygen content difference; CI = cardiac index; HR = heart rate; Max. = maximal; $\dot{Q}_c$ = pulmonary capillary blood flow; SD = standard deviation; SV = stroke volume; VO_2 = oxygen uptake.

ml at each exercise level up to 2,400 ml and thereafter increased by 100 ml for each additional exercise level. Rebreathing was initiated at functional residual capacity and continued for 8 to 12 breaths while gas concentrations were digitized and stored for off-line processing. Pulmonary capillary blood flow was estimated from the natural log of the acetylene disappearance curve.[10] Analysis was started from the breath where the concentration of helium became constant, typically the second to fourth breath, and continued through the next 4 breaths. The rebreathing protocol required a minimum of 8 breaths to mix and analyze the test gas.

$\dot{V}O_2$ in ml of O_2/kg/min was estimated as the total volume of the rebreathing compartment (lungs, rebreathing volume and dead space) multiplied by the concentration change of O_2 in the compartment over the same time interval. $\dot{Q}_c$ was calculated and divided by the time of the interval in minutes. These values were then normalized to body weight in kilograms as ml of O_2/min/kg.

Eight patients who had undergone cardiac transplantation and 11 normal volunteers were studied. Consent forms approved by the Human Subjects Review Committee at LDS Hospital were read and signed by each participant. After height and weight were measured, the subjects were seated on a Siemens electronically braked bicycle ergometer, the seat height was adjusted appropriately, and shoes were placed in toe clips. Each subject was then instructed in the use of a pneumatic balloon valve, which switched the subject from room air into the rebreathing circuit at the end of a normal expiration. Duplicate measurements of $\dot{Q}_c$ and $\dot{V}O_2$ were performed with the subject sitting on the bicycle at rest. The exercise protocol began at 25 W for 3 minutes and increased 25 W every 3 minutes thereafter until the patient was exhausted. This was a modified Bruce protocol that probably did not allow steady states to be reached at each 3-minute interval. Rebreathing tests were performed during the last minute of each exercise level. Blood pressure was recorded during every other work load. Electrocardiographic monitoring was performed to measure heart rate and observe for arrhythmias. A venous blood sample was drawn after exercise and analyzed for hemoglobin content.

Resting and maximal exercise mean values were tested for differences between the normal and transplant subjects. Plots of $\dot{V}O_2$ versus work load, $\dot{V}O_2$ versus $\dot{Q}_c$, $\dot{V}O_2$ versus heart rate, $\dot{V}O_2$ versus stroke volume, $\dot{V}O_2$ versus arterial-venous O_2 content difference ($C(a-v)O_2$) were constructed. Linear regression between the variables was performed to determine the change in each of the variables with changes in $\dot{V}O_2$.

The slope coefficients were compared between normal subjects and transplant patients by analysis of covariance to check for significant differences between the relations with $\dot{V}O_2$.

Table I lists all relevant data for the transplant patients and the control group. The 8 transplant patients (7 men) had a mean age of 31 ± 10 years (range 20 to 47), and the 11 normal subjects (10 men) had a mean age of 33 ± 7 years (range 27 to 47). The exercise studies in the transplant group were performed at a mean duration of 11.2 months (range 2 to 30) after operation.

At rest, heart rates in the transplant group averaged 98 ± 20 beats/min and were significantly higher than the normal subjects who averaged 76 ± 13 beats/min ($p = 0.0045$). Maximal heart rates were lower in the transplant patients than in the normal subjects (125 ± 21 vs 166 ± 14 beats/min, respectively, $p = 0.0095$) as were the exercise-induced heart rate increments (27 ± 13 vs 90 ± 23 beats/min, respectively, $p = 0.0010$). Maximal work rates were significantly greater in the normal than in the transplant group (94 ± 26 vs 195 ± 55 W, respectively, $p = 0.00001$).

Analysis of the hemodynamic variables listed in Table I reveals that normal subjects achieved significantly higher values than transplant patients for maximal $\dot{V}O_2$ (ml/kg/min, 34.5 ± 8.6 vs 17.6 ± 3.9 respectively, $p = 0.0006$), maximal $\dot{Q}_c$ (18.2 ± 3.6 vs 11.7 ± 3.0 liters/min respectively, $p = 0.0007$) and maximal cardiac index (9.4 ± 1.5 vs 6.0 ± 1.7 liters/min/m^2, respectively, $p = 0.0005$). Maximal $\dot{V}O_2$ tended to be smaller in the transplant group than in control subjects, although the difference between groups did not reach statistical significance (12.2 ± 1.7 vs 14.0 ± 1.4 ml of O_2/100 ml of blood, respectively, $p = 0.0863$). However, at the 25-W level of exercise, the transplant patients demonstrated a significantly higher $C(a-v)O_2$ difference than control subjects (8.92 ± 1.70 vs 7.84 ± 0.91, respectively, $p = 0.0487$). The transplant patients had a significantly lower stroke volume, expressed in ml/beat, than the control subjects at exercise levels of ≤75 W (respectively, 67 ± 22 vs 94 ± 18 at rest, $p = 0.0001$; 89 ± 33 vs 112 ± 19 at 25 W, $p = 0.0336$; 94 ± 28 vs 113 ± 17 at 50 W, $p = 0.0350$; 92 ± 27 vs 115 ± 20 at 75 W, $p = 0.0316$). There was no significant difference in stroke volumes at maximal exercise levels between transplant patients and control subjects (98 ± 36 vs 109 ± 21 ml/beat, $p = 0.1515$).

Figure 1 compares the $\dot{Q}_c$ to $\dot{V}O_2$ relation of the transplant patients with the normal group. There was no significant difference in the mean slopes of these linear relations by analysis of covariance (5.593 ± 0.475 for transplant patients vs 5.403 ± 0.130 for control subjects), suggesting that $\dot{Q}_T$ was adequately matched to O_2 consumption in the transplant patients. Significant differences were found by analysis of covariance between the transplant patients and the normal subjects for stroke index versus $\dot{V}O_2$ consumption ($p = 0.0005$) and for $C(a-v)O_2$ versus $\dot{V}O_2$ consumption ($p = 0.0329$).

Our data indicate that the cardiac transplant patients were significantly impaired in their cardiovascular response to dynamic exercise when compared with normal subjects. The lower values for maximal work load achieved and maximal $\dot{V}O_2$ reflect, in part, a state of chronic deconditioning associated with their preoperative history of cardiomyopathy and congestive heart failure. Moreover, none of the patients were engaged in formal

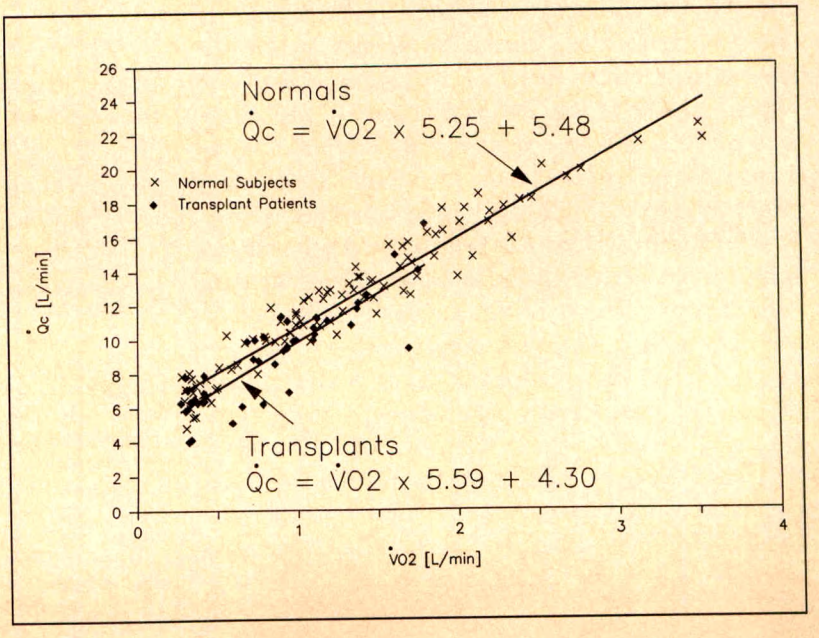


FIGURE 1. Regressions of pulmonary capillary blood flow ($\dot{Q}c$) plotted against oxygen delivery ($\dot{V}O2$) for both normal subjects and heart transplant patients.

exercise training at the time of testing. Although no evidence for graft rejection was found during the first year after surgery, chronic immunosuppressant therapy with cyclosporine, azathioprine and corticosteroids may have contributed to skeletal muscle weakness and poor exercise tolerance.

An additional important factor related to the low exercise tolerance in transplant patients is cardiac denervation and the resulting effects on exercise heart rates. Our findings are consistent with previous reports of transplant patients[1,2] showing a blunted heart rate response to exercise. Resting heart rates were significantly higher and maximal heart rates lower in the transplant patients, resulting in a small increment in heart rate from rest to maximal exercise. The small heart rate change seen in cardiac transplant patients likely had a profound effect on the cardiac hemodynamic adjustments to exercise.

The average resting heart rate of 98 beats/min in the transplant patients is consistent with what is known about the autonomic nervous system control of heart rate. In normal persons, resting heart rates are primarily due to sinus node automaticity and decrease to <100 beats/min by parasympathetic activity mediated through the vagus nerve.[12] Robinson et al[13] studied the autonomic control of heart rate during exercise in normal subjects using sympathetic and parasympathetic blocking agents. They found that the initial heart rate response to exercise, up to approximately 100 beats/min, was due to the withdrawal of parasympathetic tone, whereas increases >100 beats/min were due to increasing sympathetic tone. Studies by Rowell[14] and others[15,16] have also shown that plasma norepinephrine, an index of sympathetic activity, begins to rise during exercise when heart rates approach 100 beats/min. From these observations, it can be concluded that the higher heart rates at rest in transplant patients were due to the absence of parasympathetic innervation, and that the blunted heart rate response to exercise was due to the absence of sympathetic innervation. The delayed heart rate increase during exercise has been shown to occur as a result of circulatory catecholamines released from the adrenal medulla.[1]

Kavanah et al[17] showed that the cardiovascular response to exercise testing in transplant patients improved significantly after a structured exercise training program. Not only were peak power outputs and maximal O_2 uptakes higher after training, but the heart rate response was also improved. Resting heart rates were lower, maximal heart rates higher and heart rate increases greater after 1 to 2 years of training, suggesting that the denervated transplanted heart adapts to chronic physical activity much like a normal heart does. However, this tendency to normalize the heart rate response after training could not be explained by reinnervation. The authors speculated that the lower resting heart rates after training may be caused by reduced levels of circulatory catecholamines at rest and that the higher maximal heart rates may result from increased myocardial sensitivity to circulatory catecholamines at peak exercise.

Although there is considerable intersubject variability, the relation between $\dot{Q}_T$ and $\dot{V}O_2$ during exercise in normal subjects is reasonably stable (low intrasubject variability) and linear in the submaximal exercise range.[3] Previous studies have shown that the slope of the $\dot{Q}_T$ to $\dot{V}O_2$ relation is approximately 5 to 6 liters/min per liter of $\dot{V}O_2$.[4–6] Yamaguchi et al[18] demonstrated a rather wide intersubject variability in the $\dot{Q}_T$ to $\dot{V}O_2$ relation due to individual variations in resting and exercise hemodynamics. In their study of supine exercise, the mean slope of the $\dot{Q}_T$ to $\dot{V}O_2$ relation was 7.8 ± 1.3, significantly steeper than those reported by others,[4–6] but may have partly been due to the use of a noninvasive (ear lobe) sensing to derive dye dilution.

Our data, derived from the acetylene rebreathing technique and measured during upright exercise, were similar to previous studies and revealed no significant differences between the $\dot{Q}_T$ to $\dot{V}O_2$ slopes of transplant patients and normal subjects. Even though the transplant patients have altered hemodynamic responses to exercise, they are able to maintain their O_2-carrying capacity within normal ranges.

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Morbidity of Endomyocardial Biopsy in Cardiomyopathy

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The transvenous technique of endomyocardial biopsy was developed over 15 years ago.[1–3] Before the proliferation of heart transplant centers, this procedure was performed at only a limited number of transplant and heart failure centers in the United States. Complication rates for endomyocardial biopsy are quoted in the published reports, but detailed analyses in specific patient populations are lacking.[4–6] One retrospective study has suggested that the procedural risks differ in transplant and nontransplant patient populations.[7] The performance of endomyocardial biopsy to exclude cardiac allograft rejection is an accepted indication in heart transplant recipients. The merit of endomyocardial biopsy in diagnosing myocarditis and evaluating cardiomyopathy has been questioned because the diagnostic sensitivity of the procedure is limited and the results will not significantly influence patient management.[8–11] Therefore, clarification of the risks of this procedure in patients with unexplained heart failure allows clinicians to make informed decisions regarding the risk/benefit ratio of the procedure in specific patients. This study documents the procedural complications of endomyocardial biopsy in 706 consecutive patients with cardiomyopathy evaluated at a single institution.

Records of a consecutive series of patients with cardiomyopathic heart failure who underwent right ventricular endomyocardial biopsy between July 1981 and June 1990 were reviewed. All procedural complications were documented by a research nurse who observed the patient during and after the procedure (up to 24 hours). Since 1985, all procedures and complications have been logged in a computerized data base (474 of the 706 cases). All individual patient records were reviewed manually to be certain all complications were documented. Indications for the procedure included: (1) to rule out myocarditis, (2) to assess restrictive physiology, (3) to rule out coexistent myopathy in patients with valvular heart disease, (4) to rule out associated cardiac muscle involvement in patients with systemic disease, and (5) to assess heart failure of unknown etiology. Virtually all the patients tested had dilated or restrictive cardiomyopathy. A small group of patients (<15) with mild or no left ventricular dysfunction who were receiving anthracycline chemotherapy are included in this series.

The right internal jugular venous approach was used and the Stanford method[4] for right ventricular biopsy was followed. Bioptomes included the Scholten reusable (6.5Fr, 8Fr and 9Fr), Cordis disposable (6.5Fr, 2.4-mm cup) and Mansfield disposable (8Fr). Intraventricular electrograms were recorded to confirm the position of the bioptome in the right ventricle. A total of 4,554 specimens were obtained in the 706 patients with cardiomyopathic heart failure (6.5 per patient). Right-sided cardiac catheterization was often electively performed after the biopsy. If the operator was concerned that ventricular perforation had occurred, right-sided cardiac catheterization and echocardiography were emergently performed in the catheterization laboratory. After the procedure, patients were observed for 15 to 30 minutes in the catheterization laboratory, and inpatients were routinely visited 4 to 8 hours after the procedure. All procedures were performed by or under the direct supervi-

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*Deceased.

TABLE I Endomyocardial Biopsy Procedures

Year	Cardiomyopathy		Transplant	
	Procedures	Specimens	Procedures	Specimens
1981–82	83	449 (5.4)*	—	—
1982–83	33	188 (5.7)	—	—
1983–84	43	320 (7.4)	—	—
1984–85	73	457 (6.3)	—	—
1985–86	118	875 (7.4)	—	—
1986–87	116	663 (5.7)	125	977 (7.8)
1987–88	99	709 (7.2)	218	1,045 (4.8)
1988–89	76	495 (6.5)	276	1,371 (5.0)
1989–90	65	398 (6.1)	339	1,829 (5.4)
Total	706	4,554 (6.5)†	958	5,222 (5.5)

*Values in parentheses represent biopsy specimens per patient.
†$p = 0.002$. A significantly greater number of biopsies were performed per patient in the cardiomyopathy group than in the transplant group.

TABLE II Endomyocardial Biopsy Complications

	Cardiomyopathy (n = 706)	Transplant (n = 958)
Major	6 (0.85%)	2 (0.21%) p = 0.06
Minor	18 (2.6%)	1 (0.1%) p = 0.0001
Overall	24 (3.4%)	3 (0.31%) p = 0.0001

sion of 1 of 4 attending cardiologists (RCS, DVF, DFH, DVU) experienced in the procedure of endomyocardial biopsy.

Procedural complications in the cardiomyopathic heart failure (nontransplant) patient group were compared with those seen in a group of adult orthotopic cardiac transplant recipients. This control group comprised 55 consecutive orthotopic cardiac transplant recipients who underwent 958 endomyocardial biopsy procedures between August 1986 and June 1990. The indication for the biopsy in all the control patients was to rule out cardiac allograft rejection. The right internal jugular venous approach was used in 955 of the 958 procedures. In 3 procedures the right femoral venous approach to right ventricular biopsy was followed and a bioptome guiding sheath was used.[12] A total of 5,222 specimens were obtained during the 958 procedures (5.5 per patient). All other aspects of the procedure were identical to those described in the study group of patients with cardiomyopathic heart failure.

Data are presented as mean ± standard deviation. The incidence of complications in the 2 patient groups were analyzed in 2 × 2 contingency tables by the chi-square test (without the continuity correction). Statistical significance was defined as $p < 0.05$.

Table I summarizes the biopsy procedures performed over a 9-year period. Twenty-seven complications were observed during 1,664 procedures; 24 occurred in cardiomyopathy patients and 3 in transplant patients (Table II). No deaths were attributed to a procedure-related complication. "Major complications" were defined as events that required interventions resulting in hospitalization or prolongation of the hospital stay. Six major complications were observed in biopsy procedures performed in 706 patients with cardiomyopathic heart failure and 2 complications were seen in procedures performed in 958 transplant patients. The difference in the incidence of major complications between the 2 groups was not statistically significant ($p = 0.06$). Eighteen minor complications occurred in the cardiomyopathy group. "Minor complications" were defined as those that could be managed immediately in the catheterization laboratory and required observation that did not result in hospitalization or prolongation of the hospital stay. The presence of minor complications was greater in the cardiomyopathic heart failure group than in the transplant group. The incidence of specific complications in both groups is summarized in Table III. The 24 complications in the cardiomyopathy group and their management are depicted in Figure 1.

This study documents that the overall complication rate of endomyocardial biopsy is 3.4% in patients with cardiomyopathy. In comparison, the risk of a complication in cardiac transplant recipients is 0.31%, which represents a significantly lower incidence ($p = 0.0001$). No ventricular perforations were observed in any of the cardiac transplant recipients. This is an important observation that should be considered when the risk of the endomyocardial biopsy procedure is evaluated. In 1978, Mason[4] reported 4 cases of cardiac perforation with tamponade in >1,300 procedures (0.31%). Most of the procedures were performed in transplant recipients, and complication rates in different patient groups were not defined. In 1984, a Stanford series documented that cardiac tamponade had occurred 4 times in >4,000 procedures (0.14%), again presumably primarily in transplant recipients.[6] Consistent with our observations, Anastasiou-Nana et al[7] reported that the incidence of cardiac perforation in 243 nontransplant patients was 0.82% (2 of 243), compared with no perforations in 704 proce-

TABLE III Complications with Endomyocardial Biopsy: 1,664 Procedures with 9,776 Biopsies

Complications	No.	% Total	% CHF	% Tx	p Value*
Ventricular perforation	6				
Per procedure		0.36	0.85	0	<0.005
Per biopsy specimen		0.06	0.13	0	<0.01
Pneumothorax	4†	0.24	0.28	0.21	NS
Vasovagal reaction	7	0.42	0.99	0	<0.005
Ventricular tachycardia	4	0.24	0.57	0	<0.025
Atrial flutter	3‡	0.18	0.28	0.10	NS
Atrial fibrillation	1	0.06	0.14	0	NS
Transient RBBB	1	0.06	0.14	0	NS
Transient AV dissociation	1	0.06	0.14	0	NS

*Significance of difference in occurrence of complications in transplant patients with cardiomyopathic heart failure.
†Pneumothorax occurred in 2 transplant patients.
‡Atrial flutter occurred in 1 transplant patient.
AV = atrioventricular; RBBB = right bundle branch block; CHF = cardiomyopathic heart failure; NS = not significant; Tx = cardiac transplant.

lures in transplant patients. These data suggest that endomyocardial biopsy may be a higher-risk procedure n nontransplant (cardiomyopathy) patients.

The present study accurately depicts the true incidence of complications associated with the endomyocardial biopsy procedure in patients with cardiomyopathy. Prior series inaccurately reflected the complication rate because disparate and small patient populations were studied. It should be recognized that the risks are higher in patients with cardiomyopathy. Nonetheless, the actual incidence of major complications in patients with cardiomyopathy remains extremely low.

Experience with the procedure appears related to safety. All biopsies in the first year were performed by a single operator (DVU). His learning curve represents 83 cases with 3 perforations, an incidence of 3.6%. This operator subsequently trained the other operators (RCS, DVF, DFH). Three perforations occurred during the next 623 cases, an incidence of 0.48% ($p = 0.0035$). Two of the 3 perforations occurred when a trainee who was not committed to the mastery of this technique performed a sporadic case. It is impossible to calculate the true incidence of complications by comparing experienced and inexperienced operators because virtually all endomyocardial biopsies are performed by an experienced attending cardiologist at our institution. Three points should be emphasized: (1) a "learning curve" is associated with safety and trainees should be very carefully supervised, (2) complications are low for experienced operators performing a high volume of procedures, and (3) serious complications are more frequent for inexperienced operators. One would expect an even higher complication rate by inexperienced operators performing few and unsupervised procedures.

The true incidence of complications and the safety of performing endomyocardial biopsy in patients with cardiomyopathy are relevant issues. The need to perform heart biopsy in this patient population has been questioned.[9-11,13-16] The ability of endomyocardial biopsy to diagnose myocarditis and to assess whether immunosuppression is an efficacious therapy remains unresolved. Although endomyocardial biopsy is often a low-yield

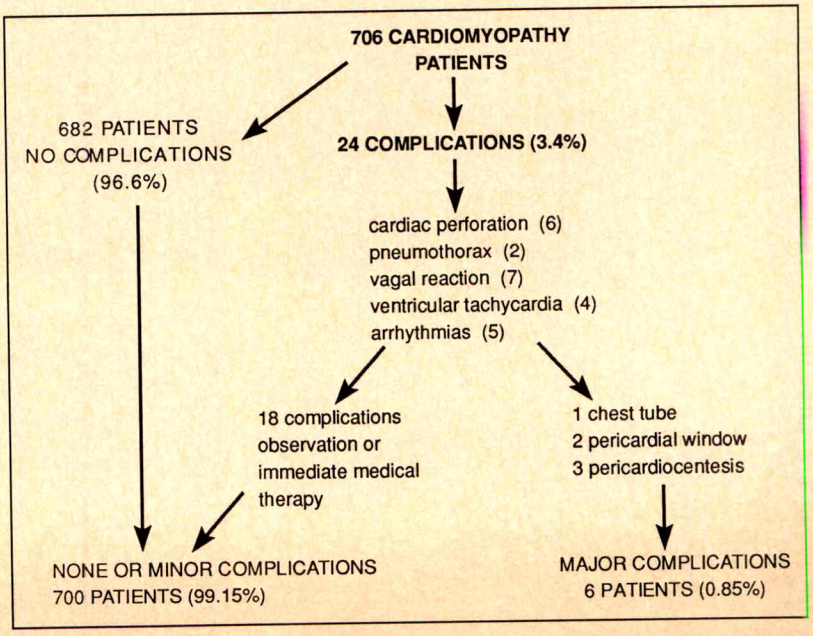


FIGURE 1. Twenty-four complications occurred in conjunction with endomyocardial biopsy performed in 706 patients with cardiomyopathy. The frequency of each complication and its management is depicted. Major complications resulted in hospitalization or prolongation of hospitalization.

invasive procedure performed to diagnose diseases (e.g., myocarditis and amyloid heart disease) with unproved therapy, it has extremely low morbidity when performed by experienced operators. The potential hazards of immunosuppressive therapy in patients without biopsy-proved myocarditis far exceed the risk of the endomyocardial biopsy procedure. We believe the safety of this technique in experienced hands justifies its continued use. Only additional clinical experience and laboratory data can provide answers and define the role and clinical relevancy of this procedure.

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Protein C Deficiency and Acute Myocardial Infarction in the Third Decade

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Protein C deficiency has been associated with a predisposition to venous thrombosis and thromboembolism. Arterial thrombosis has been seen much less frequently and may require other vascular risk factors. Here we describe a young patient with protein C deficiency presenting with an acute myocardial infarction (AMI).

A 28-year-old white man, with a history of cardiac contusion, was transferred on June 22, 1990 for further management after an AMI. On March 24, 1989, 15 months before his AMI, the patient sustained a myocardial contusion from a motor vehicle accident. This was manifested by a transient right bundle branch block, which appeared to have resolved on subsequent electrocardiograms. After this episode he was asymptomatic until June 19, 1990, when he developed substernal chest pressure radiating to the left shoulder, with diaphoresis, nausea and vomiting. Electrocardiogram revealed Q waves in leads I and aVL, and 2-mm ST elevation in leads I, aVL, and V_3 to V_6. Eight hours after the onset of pain he received recombinant tissue-type plasminogen activator intravenously. The pain persisted and he underwent emergency cardiac catheterization, which revealed a thrombus in the left main coronary artery, a large normal right coronary artery, and a small normal left circumflex coronary artery. Intracoronary recombinant tissue-type plasminogen activator and systemic streptokinase were given. Creatine phosphokinase peaked at 4,200 IU. He was administered nitroglycerin, full-dose heparin and lidocaine, and was transferred to our hospital.

As a child he had asthma. He was receiving no medications at the time of presentation. There was a 15 pack-year history of cigarette use but he had not smoked in the preceding 2 years. He worked as a machine operator and denied alcohol or drug abuse. His family history was remarkable for a father with protein C deficiency based on a history of recurrent thromboembolism and a protein C activity of 47%. His paternal uncle died from AMI at age 35 years. Two follow-up cardiac catheterizations revealed a marked decrease in the size of the left main thrombus, with apical akinesia and otherwise normal myocardial wall motion. He was discharged while receiving warfarin, atenolol and aspirin. His first protein C antigen level obtained while he was in the hospital and receiving heparin was depressed at 51% (normal 70 to 130%, Southeastern Wisconsin Hemostasis Laboratory). The total protein S was normal at 90%, whereas the free protein S was slightly depressed at 63%. The factor X was normal at 76%. The protein C antigen level was repeated 4 weeks later and remained depressed at 54%. The antithrombin III level was normal at 95% (normal 86 to 140%). His total cholesterol was 167 mg/dl, triglyceride level 129 mg/dl, high-density lipoprotein 44 mg/dl and low-density lipoprotein 102 mg/dl. During the hospitalization his hemoglobin was 13.9 g/dl, hematocrit was 40%, and platelet count varied from 200,000 to 494,000 per μl (normal 200,000 to 400,000/μl). There was no evidence of liver disease or vitamin K deficiency, as the transaminases were normal, albumin was 4.5 g/dl, and coagulation studies revealed a prothrombin time of 12.4 seconds and a partial thromboplastin time of 27.4 seconds. His fibrinogen was 311 mg/dl and fibrin split products were <8 μg/ml. The Westergren sedimentation rate was normal at 12 mm/hour.

Protein C deficiency is a hereditary disorder transmitted in a codominant fashion. Heterozygous persons have <60% of normal plasma levels of protein C, whereas homozygous persons have no detectable levels of protein C. The homozygous state usually presents in the neonatal period as a devastating disease called purpura fulminans neonatalis. The heterozygous state generally comes to clinical attention in the late teens or early twenties, manifested as superficial thrombotic episodes, deep venous thrombosis, pulmonary embolus or, less frequently, arterial thrombosis.

The anticoagulant protein C and its cofactor, protein S, require vitamin K for the post-translational step that adds a γ-carboxyl group to glutamic acid residues. This step occurs in the liver and is inhibited by warfarin. Procoagulant factors such as II, VII, IX and X also must undergo this carboxylation to function as procoagulants. Except for protein S, all of the vitamin K-dependent proteins circulate as zymogens that must be cleaved to form active serum proteases. Protein C is activated by an interaction between thrombin and thrombomodulin at the surface of the endothelial cell. Thrombomodulin is an intrinsic membrane protein

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of the endothelial cell. When thrombin binds to thrombomodulin, protein C is cleaved and activated much more readily than in the circulation. The majority of activation occurs in the capillary beds, where the proportion of endothelial cell surface (and therefore thrombomodulin) to circulating blood volume is high. Activated protein C acts as an anticoagulant by cleaving and inactivating factors V and VIII, which normally serve to promote the activity of factor Xa and IXa, respectively. Activated protein C has also been shown to increase the activity of the fibrinolytic system. Protein C therefore represents a mechanism for the endothelial cell surface to maintain a hemostatic balance, and deficiency of the factor would create an increased tendency for thrombosis.

Protein C deficiency is well known to be associated with thromboembolic disease.[1] Although most reported cases of thromboses have occurred in the venous system, arterial thrombosis has occurred on occasion.[2] Coller et al[3] described a 28-year-old man with protein C deficiency and a smoking history who had recurrent deep venous thromboses, pulmonary embolism and AMI. Cardiac catheterization at the time of AMI revealed a thrombus occluding the left anterior descending coronary artery, without coronary atherosclerosis. This patient had coronary artery bypass surgery and was discharged while receiving warfarin. The patient later discontinued warfarin on his own and developed left radial and ulnar artery occlusions.

A report in 1987 estimated that 1 in 300 adults are heterozygous for protein C deficiency, although low protein C levels did not, by themselves, appear to explain an increased risk of thrombosis.[4] It is likely that other factors in addition to protein C deficiency contribute to the development of thrombosis, such as damaged endothelium, vascular stasis, or other imbalances between procoagulants and anticoagulants. Therefore, any injury to the endothelial cells that affects proper expression of thrombomodulin, synthesis of protein S, or Va inactivation could potentially lead to a hypercoagulable state and thrombotic complications in the presence of a low protein C level.

The preceding cardiac contusion may have predisposed our patient to his AMI. Although the contusion occurred 15 months before the infarction, blunt chest trauma has been associated with late coronary artery stricture presenting 10 months later.[5] Cardiac contusion with delayed AMI in a protein C-deficient patient has never been reported.

It appears that this patient's protein C deficiency in the presence of other vascular risk factors (i.e., contusion, remote history of cigarette smoking and a family history of premature AMI) may predispose to early AMI. Furthermore, young patients with AMI and a family history suggestive of hypercoagulability should undergo hematologic evaluation, including a check of protein C levels. In patients diagnosed with protein C deficiency and a history of recurrent thromboembolism, warfarin would be the therapy of choice to prevent subsequent episodes of thrombosis.

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Upright Retrograde P Waves During Ventricular Tachycardia

Ray Parkin, MB, BS, George Nikolic, MB, BS, and David H. Spodick, MD, DSc

The morphology and axis of retrograde atrial activation have been well defined: a negative deflection in leads II, III and aVF, reflecting a frontal plane axis of −31 to −100 degrees.[1,2] Retrograde P waves upright in the same leads are well documented[3] but exceedingly rare in clinical electrocardiography. When observed in association with broad ventricular complexes, they can be mistaken for upright P waves of sinoatrial initiation and can be responsible for resulting misdiagnoses.[4] An example of ventricular tachycardia with positive yet undoubtedly retrograde P waves is described below.

The patient, a 63-year-old man, had prolonged weakness and lightheadedness at rest with diaphoresis, dizziness and blurred vision, but no chest pain. These symptoms recurred in a milder form 9 years after a myocardial infarction. Electrocardiography revealed ventricular bigeminy with occasional runs of ventricular tachycardia. He was given lido-

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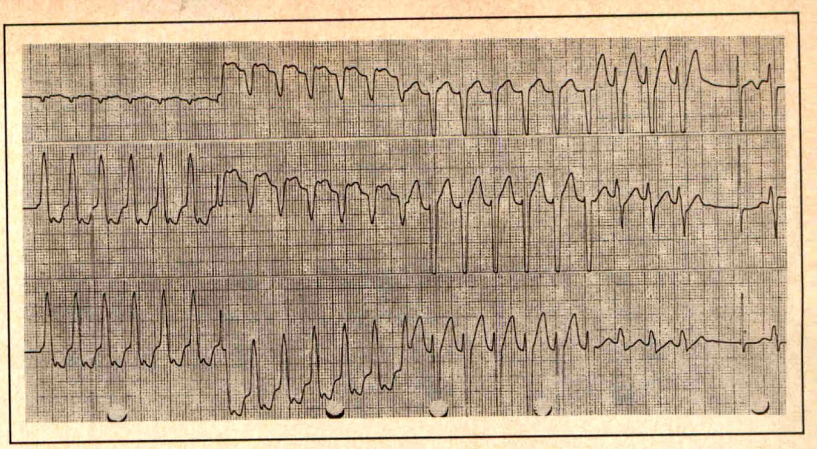


FIGURE 1. Twelve-lead electrocardiogram revealing upright retrograde P waves in the limb leads. The last complex of the paroxysm is a retrograde P wave, seen as a biphasic atrial complex in lead V_6. See text.

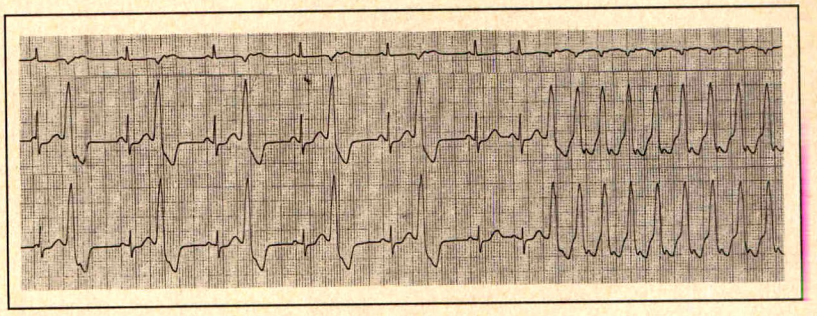


FIGURE 2. Rhythm strip of standard leads I, II and III, recorded simultaneously. See text.

caine, and admitted. Blood pressure was 116/50 mm Hg; heart rate was 64 beats/min. The initial electrocardiogram revealed frequent ventricular ectopic beats in bigeminy, incomplete right bundle branch block and T-wave inversion in leads V_1 to V_3. Chest x-ray revealed a normal heart and vasculature. Recurrent bigeminy and prolonged runs of ventricular tachycardia prompted us to increase lidocaine to 4 mg/min with no evidence of toxicity; ventricular ectopic activity progressively decreased and disappeared. Figures 1 and 2 were obtained during arrhythmia.

Figure 1 shows a broad complex (0.14 second) tachycardia slowing from 154/min to 142/min before stopping in leads V_4, V_5 and V_6; a junctional escape beat and a ventricular complex identical to those of the preceding tachycardia terminate the tracing. The ventricular complexes have typical left bundle branch block morphology in the chest leads and could be pronounced aberrant by standard criteria[5] were it not for the right-axis deviation in the limb leads. Such axis deviation in association with left bundle branch block has not been seen in aberrant conduction to date.[6]

Atrial activity is only clearly discernible in the limb leads and in V_6. P waves follow the QRS with RP intervals at 0.16 second; they are upright in leads I, II, III and aVF, and are possibly biphasic in V_6. So far, there is no evidence that this is not an atrial tachycardia with first-degree atrioventricular block and a unique left bundle branch block aberrancy rather than ventricular tachycardia with the rare form of retrograde atrial activation.

The proof that the P waves are not initiated in the sinus or atrium is in Figure 2, where ventricular ectopic beats in bigeminy progress to ventricular tachycardia. In the presence of sinus P waves, the narrower and more pointed retrograde P waves occur only after the broad complexes. Most of our current understanding of P-wave polarity in retrograde atrial activation comes from the work of Waldo et al.[3] Waldo's observations, however, are not necessarily applicable to our case, because his studies did not involve spontaneous infranodal rhythms. For retrograde P waves upright in the inferior leads, the sequence of atrial activation involves rapid conduction through the anterior internodal tract to Bachmann's (interatrial) bundle, with subsequent spread "in a manner similar to that which occurs during normal sinus rhythm . . . ."[3]

Positive retrograde P waves are a rare but important variant of retrograde atrial activation. They can be diagnosed by using the surface electrocardiogram when there is an opportunity to observe the onset or termination of the causal ventricular or junctional rhythm. We hope that reports of further examples will strengthen its recognition in clinical electrocardiography.

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Prospective Identification by Two-Dimensional Echocardiography of Anomalous Origin of the Left Main Coronary Artery from the Right Sinus of Valsalva

Barry J. Maron, MD, Martin B. Leon, MD, Julie A. Swain, MD, Richard O. Cannon III, MD, and Antonio Pelliccia, MD

Anomalous origin of the left main coronary artery (LMCA) from the right (anterior) sinus of Valsalva has been the coronary anomaly most frequently associated with sudden catastrophes in youthful athletes.[1–3] This malformation is rarely identified during life and usually is initially recognized only at autopsy. Recently, there has been interest in the usefulness of echocardiography in the preparticipation screening of competitive athletic populations.[4,5] We report on a young athletic man in whom a potentially lethal coronary arterial anomaly was recognized prospectively by echocardiography, permitting elective surgical intervention.

At initial evaluation, the patient was a healthy 21-year-old male college senior. He was extremely active, participating in a number of sports, including a rigorous jogging program. In the previous 4-month period, however, he had 4 syncopal spells associated with exertion. No precordial murmur or click was audible. Echocardiographic dimensions (in mm) were: ventricular septal and posterior wall thicknesses, 13; left atrium, 32; aorta, 28; left ventricular dimensions, 48 at end diastole and 25 at end systole. Effort was made to image the LMCA prospectively, at its origin from the left coronary sinus, using cross-sectional views of the aorta from the parasternal and apical windows[6]; however, no area of discontinuity could be demonstrated in the circumference of the aortic root at the aortic valve level (Figure 1). In addition, by angulating the transducer superiorly, it was possible to image the ostia and the proximal segments of 2 coronary arteries (presumably the LMCA and right coronary artery) emanating from the anterior sinus

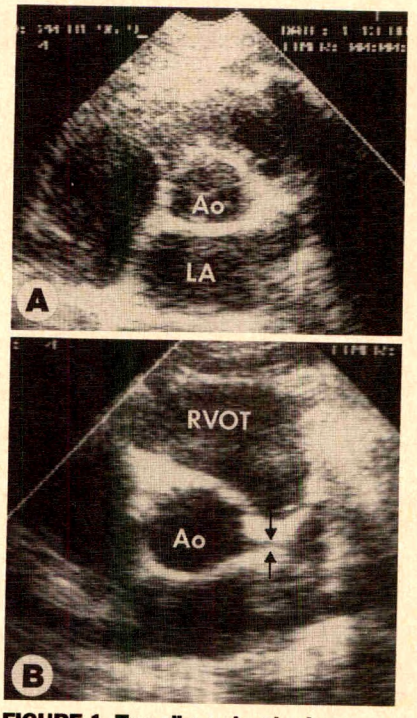


FIGURE 1. Two-dimensional echocardiographic cross-sectional images of the aortic root. *A*, the ostia and proximal left main coronary artery of our 21-year-old patient could not be imaged and the circumference of the aortic root remained intact, even after transducer angulation. *B*, for comparison, a normal 21-year-old athlete in whom the origin and proximal segment of the left main coronary artery were easily imaged *(arrows)*. Ao = aorta; LA = left atrium; RVOT = right ventricular outflow tract.

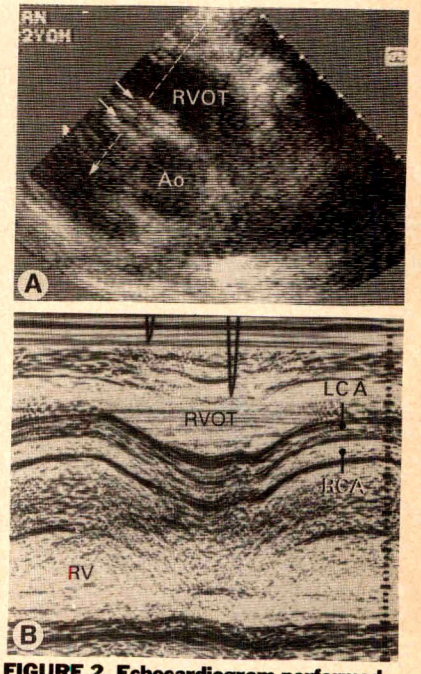


FIGURE 2. Echocardiogram performed from our patient's third left intercostal space with the transducer angulated superiorly to image the ostia of the right coronary artery (RCA). *A*, 2 separate lumen and arterial segments appear to arise from the aorta (Ao) at the 11 o'clock position *(arrows)*. *Broken line* denotes path of derived echo beam generating the image shown in *panel B*. *B*, M-mode echocardiogram demonstrates parallel structures consistent with 2 separate coronary lumen; calibration marks are 1 mm apart. LCA = left coronary artery; RV = right ventricle; other abbreviation as in Figure 1.

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of Valsalva (Figure 2); these vessels appeared to be parallel and to have separate ostia.

The electrocardiogram revealed left ventricular hypertrophy with "strain" pattern and "giant" T-wave inversion in the precordial leads (up to 17-mm deep); predominant R wave was present in V_1. During the recovery phase of an exercise test, he suddenly experienced sinus bradycardia (20/min) followed by sinus arrest and syncope. While hospitalized for 6 days, the patient demonstrated no ectopic activity on telemetry. Cardiac catheterization revealed (in mm Hg): aorta, 120/70; left ventricle, 120/13; right ventricle, 17/5; pulmonary artery, 22/11; left atrium, 11. Electrophysiologic studies were normal.

Selective coronary angiography confirmed that both the right coronary artery and the LMCA originated from the right (anterior) coronary sinus, and from adjacent but separate ostia. The LMCA appeared to be anterior to the right coronary artery and it coursed posteriorly between the aorta and the pulmonary artery (Figure 3). The sinus node artery branch originated from the circumflex artery rather than from the right coronary artery; the right coronary system was dominant. Luminal narrowing by atherosclerosis was absent. The patient underwent coronary artery bypass surgery with an end-to-end anastomosis of the left internal mammary to the left anterior descending coronary artery; coronary arteries were not ligated.

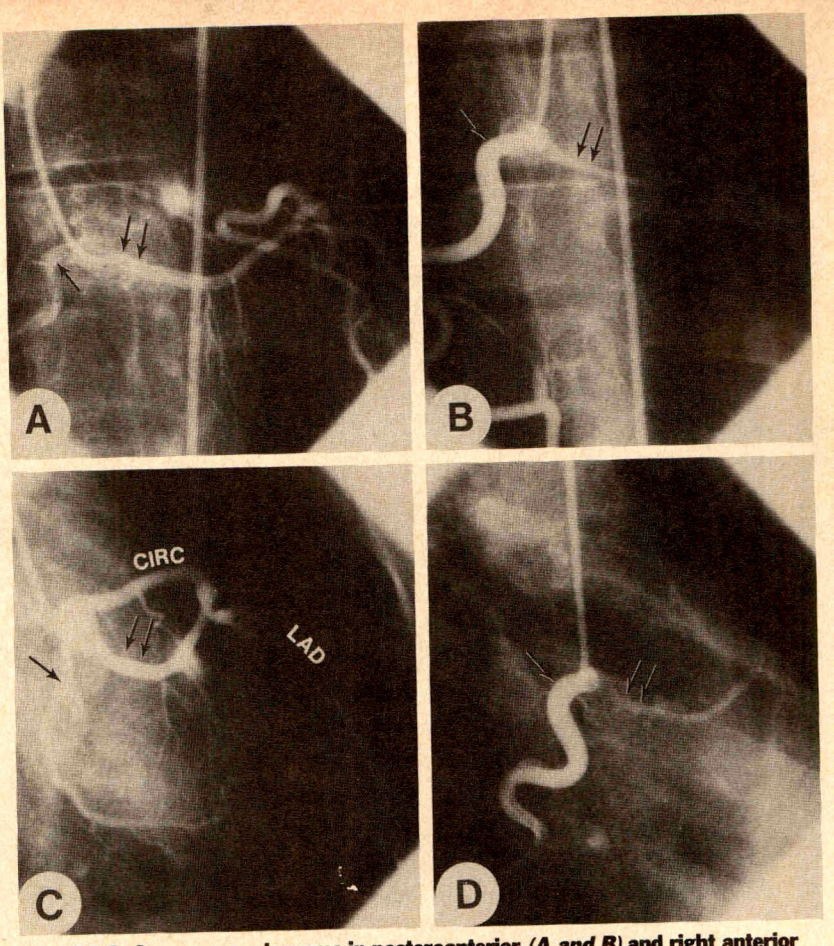


FIGURE 3. Coronary angiograms in posteroanterior *(A and B)* and right anterior oblique *(C and D)* views demonstrating selective cannulation and injection of the right coronary ostium *(single arrow)* and the left main coronary ostium *(double arrows)*, both arising from the right (or anterior) coronary sinus. Left lateral projection (not shown) demonstrated the left main coronary artery to be directed posteriorly between the pulmonary artery and aorta, an anatomic relation that was confirmed intraoperatively. Circ = circumflex; LAD = left anterior descending artery.

Anomalous origin of the LMCA from the anterior sinus of Valsalva is rarely diagnosed during life, primarily because clinical diagnosis requires a high index of suspicion. Nevertheless, identification is critical because it is an anomaly that is potentially correctable by operative revascularization.[1] The observations made in our patient support the usefulness of 2-dimensional echocardiographic imaging in prospectively identifying anomalous origin of the LMCA. In a youthful athletic population, in which the quality of echocardiographic studies and resolution of cardiac anatomy is generally high, it is possible to image the origin and proximal segment of the LMCA in a high percentage of cases (probably >90%).[4] Therefore, failure to demonstrate the LMCA arising from its usual position in the left coronary sinus in a young person with impaired consciousness (e.g., syncope) should create heightened suspicion of this anomaly[2] and suggest the necessity of anatomic documentation with coronary arteriography.

In our patient, the correct diagnosis of an anomalous LMCA was strongly suggested by echocardiography *before* selective coronary arteriography. This suspicion arose after complete interrogation of the aortic wall in the short-axis plane failed to identify an area of discontinuity in the aortic root circumference at the 4 or 5 o'clock position, which would have been consistent with the ostia and proximal segment of the LMCA. Subsequent imaging revealed that both left and right coronary arteries arose from the anterior coronary sinus. Our success in prospectively identifying an anomalous

LMCA in this patient underlines the importance of imaging the LMCA origin as part of the routine echocardiographic evaluation of young competitive athletes.

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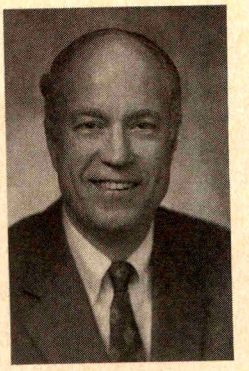
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The Government is in *Your* Office and Listening to *Their* Script



Pharmaceutical representatives for some time have been limited in the USA in what they can say about their products to physicians. The government — and rightly so — has decreed that they must limit their statements concerning indications for their products to those described in the package insert included with their product. Now physicians can be told what they can say to their patients.

Some background. In 1970, Congress enacted the family planning program known as Title X of the Public Health Service Act. It provided federal grants to some family-planning clinics, including Planned Parenthood, and now costs $144 million annually. In the 2 decades since then, the federal government has interpreted the law first to *permit* (1971), then to *require* (1976), and finally to *forbid* (1988) clinic workers to discuss the abortion option with their patients. On 23 May 1991 the Supreme Court ruled in the case *Rust v. Sullivan* to uphold the 1988 interpretation of the 1970 family planning law. The Supreme Court thus approved the following regulations:

"A Title X project may not provide counseling concerning the use of abortion as a method of family planning or provide referral for abortion as a method of family planning.

"Once a client is diagnosed as pregnant, she must be referred for appropriate prenatal and/or social services by furnishing a list of available providers that promote the welfare of mother and unborn child."

"A Title X project may not use referrals as an indirect means of encouraging or promoting abortion by including on the list of referral providers health care providers whose principal business is the provision of abortions or by 'steering' clients to providers who offer abortion.

"A Title X project must be organized so that it is physically and financially separate from (abortion) activities."

Dr. Irving Rust, who brought the case through the courts, is the medical director of a Planned Parenthood family-planning clinic in the South Bronx. A Harlem-raised physician, Dr. Rust had worked since 1981 with the guidelines that forbid the use of federal funds to perform abortions. But in 1988, when the Reagan administration wrote the regulations for Title X that banned even talking about abortion, he balked. As Dr. Rust said in 1990, what was at stake was the relationship between a physician and a patient, the ability to talk freely and honestly. "If a woman came in with cancer of the ovary and there were three methods of treatment," he explained as an analogy, "could I tell her the government says that chemotherapy is *the* treatment, no matter what I think?" In other words, as the new Justice David Souter remarked, the government in effect may preclude professional speech.

The Supreme Court's 5-4 decision forbids anyone who works in one of the 4,000 federally funded clinics that provide family planning to 4 million poor American women from using the word "abortion." If a patient asks about abortion, he or she must read from the federal script: "The project does not consider abortion an appropriate method of family planning." If the patient then asks for referral, there are more scripts. Her physician or provider has to refer her for prenatal care to those who "do not perform abortions." Thus, as Ellen Goodman has put it: "a concrete crisis in the life of a poor woman becomes an abstraction in the words of the justices."

The *Rust v. Sullivan* case is not a case about whether abortion should be legal. Like it or not, it is legal. This is rather a case about whether it is permissible to talk about abortion in a federally funded clinic. Thus, for the first time in history, the Supreme Court has prohibited the expression of a certain viewpoint in a government-sponsored setting. This edict is clearly wrong and even scary. As Michael Gartner has expressed it: "We are all dependent on the government for economic support. Farmers get subsidies. Will they be told they can't talk about the dangers of chemicals or complain about the weather? Bankers get deposit insurance. Will they be told they can't criticize the Fed or talk about a recession? Newspapers get a break on postage. Will they be told they can't write about the Pentagon or editorialize about the Supreme Court?" Clearly our cherished freedom of speech is being affected by this court decision.

Possibly some of the regulations will change. Congress is now moving with unusual speed to act on legislation that will reverse this recent Supreme Court decision upholding the government's ban on abortion counseling at federally funded family planning clinics. According to a recent Washington Post-ABC News Poll, 63% of Americans favor allowing the staff of federally funded family planning clinics to mention abortion as an option to pregnant women.

Tomorrow it may be cardiologists, not obstetricians, who are told what they may say to their patients.



William Clifford Roberts, MD
Editor in Chief

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Cole D. Get government out of the doctor's office. *The Washington Post*, May 28, 1991.
McCarthy C. The courts' consistency. *The Washington Post*, May 30, 1991.
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Dewar H. Hill moves briskly on abortion bills. *The Washington Post*, June 4, 1991.

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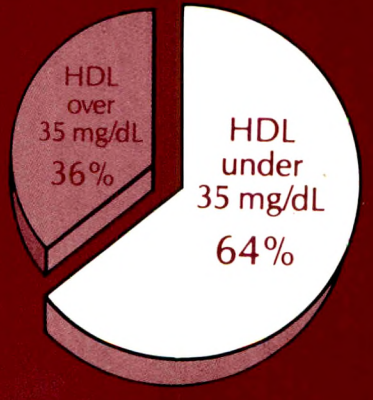
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CORONARY ARTERY DISEASE

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Outcome of Patients Who Were Admitted to a New Short-Stay Unit to "Rule-Out" Myocardial Infarction

Jean-Michel Gaspoz, Thomas H. Lee, E. Francis Cook, Monica C. Weisberg, and Lee Goldman

For emergency room patients with a low probability of acute myocardial infarction, we established a new short-stay coronary observation unit, a 2-bed nonintensive care unit with telemetry monitoring adjacent to the emergency room. Of 512 admissions to the coronary observation unit, 83% were discharged home without evidence of acute myocardial infarction or serious complications (mean length of stay, 1.2 days); 17% were transferred to other hospital beds. The rate of acute myocardial infarction was 3%. No deaths and only 1 complication occurred in the coronary observation unit; at 6-month follow-up the cardiac survival rate was 99% for the patients sent home directly from it. The coronary observation unit is safe and adequate for ruling out acute myocardial infarction in a defined subset of patients. Short-stay units, however, encourage early discharges which, when premature, may miss patients who have complications shortly thereafter; mandatory but expeditious predischarge stress testing may augment the efficiency of such units.

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Beneficial Effect of Long-Term Beta Blockade After Acute Myocardial Infarction in Patients Without Anterograde Flow in the Infarct Artery

D. Brent Glamann, Richard A. Lange, and L. David Hillis

Long-term survival after acute myocardial infarction (AMI) is improved by β-adrenergic blockade and anterograde flow in the infarct artery. To assess the influence of β blockade on mortality in survivors of AMI without anterograde flow, 113 subjects with AMI and no anterograde flow in the infarct artery and no disease of the other arteries were medically treated for 48 ± 28 (mean ± standard deviation) months. Forty-six patients received long-term β blockade, whereas 67 did not. Of the 46 subjects given β blockers, 1 (2%) died of cardiac causes; in contrast, 20 (30%) of the patients not given β blockers died of cardiac causes ($p = 0.007$ compared with group I). Thus, in survivors of AMI without anterograde flow in the infarct artery, mortality is markedly reduced by long-term β blockade.

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Issued: March 1991

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Diurnal Variations of Neurocardiac Rhythms in Acute Myocardial Infarction

Markad V. Kamath and Ernest L. Fallen

Using power spectrum analysis of heart rate (HR) variability, this study examined diurnal variations of neurocardiac rhythms in 24 patients with acute myocardial infarction. There were no differences in HR, HR variability or the low-frequency (sympathetic) peak power during any temporal sequence throughout the day. In the 14 patients not taking β blockers, the high-frequency (vagal) component was significantly increased during late evening hours, whereas the low-frequency (primarily sympathetic) component was dominant during early morning and midafternoon hours. Beta blockade appeared to suppress any diurnal variation of neurocardiac rhythms as measured by the HR autospectrum. Data suggest that ≥ 2 sympathetic surges occur diurnally in patients during the early stages of acute myocardial infarction, although β blockade appears to blunt circadian cardiac rhythms.

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Coronary Recanalization Rate After Intravenous Bolus Administration of Alteplase in Acute Myocardial Infarction

Bernardino Tranchesi, Jr., Dalton F. Chamone, Christa Cobbaert, Frans Van de Werf, Philippe Vanhove, and Marc Verstraete

We evaluated the effectiveness and safety of an intravenous 70-mg (or 80-mg if body weight ≥ 90 kg) bolus dose of alteplase (predominantly single-chain recombinant tissue-type plasminogen activator) in 60 patients with acute myocardial infarction with an angiographically demonstrated occluded infarct-related coronary artery. The recanalization rate at 90 minutes was 48% (95% confidence interval, 37 to 60%). Minor bleeding was observed in 65% (95% confidence interval, 53 to 75%) of patients and occurred primarily at puncture sites. A single intravenous bolus dose of 70 or 80 mg of alteplase does not appear to be an optimal dosage regimen in the treatment of acute myocardial infarction.

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Older Age and Elevated Blood Pressure Are Risk Factors for Intracerebral Hemorrhage After Thrombolysis

Jeffrey L. Anderson, Labros Karagounis, Ann Allen, Mark J. Bradford, Ronald L. Menlove, and T. Allan Pryor

Risk factors were assessed for intracerebral hemorrhage occurring after thrombolytic therapy given for acute myocardial infarction. Intracerebral hemorrhage occurred in 4 of 107 treated patients at 3.5 to 48 hours after beginning therapy and was fatal in 2. Patients with intracerebral hemorrhage were older (77 ± 7 vs 62 ± 11 years, $p = 0.01$), and had higher initial (161 ± 23 vs 135 ± 23 mm Hg, $p = 0.03$) and maximal (171 ± 30 vs 146 ± 20 mm Hg, $p = 0.02$) systolic blood pressures; diastolic blood pressure also tended to be higher. Differences were not significant for gender, height, weight, site of infarction, thrombolytic agent and concomitant therapy. Age >70 years and blood pressure $\geq 150/95$ mm Hg defined

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Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section). Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section). Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section in the complete prescribing information.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil*, and *amiodarone* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since this may impair the excretion of digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in anima to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted wi digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or ca affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. Howe er, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, th amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digo in is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS sectio and Serum Digoxin Concentrations subsection of DOSAGE AND ADMINISTRATION). The overall incidence of advers reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of pa tients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of th serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-hal gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these advers reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, a the most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (noda rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degre may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbance Digoxin may also induce other changes in the ECG (e.g. PR prolongation, ST depression), which represent digoxi effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosag However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdomin pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy and psychosis can occu

Other—Gynecomastia is occasionally observed. Maculopapular rash or other skin reactions are rarely observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhe and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliab signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conductio disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junction (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impendin digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteratio in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digo in intoxication.

OVERDOSAGE:

Treatment of Arrhythmias Produced by Overdosage:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessa if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Correction of factors that may contribute to toxicity such as electrolyte disturbances, hypoxia, acid-base disturbance and removal of aggravating agents such as catecholamines, should also be considered. Potassium salts may be ir dicated, particularly if hypokalemia is present. Potassium administration may be dangerous in the setting of massiv digitalis overdosage (see Massive Digitalis Overdosage subsection below). Potassium chloride in divided oral dose totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (se below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium shou be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentratio of 40 mEq per 500 mL) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to loc irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitorin should be performed to watch for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effe on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, atropine and/ temporary ventricular pacing may be beneficial. Digibind®, Digoxin Immune Fab (Ovine), can be used to reverse potential life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usual begins within ½ hour of Digibind administration. Each 40 mg vial of Digibind will neutralize 0.6 mg of digoxin (whic is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced b overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour ma be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enoug to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modificatio because of individual sensitivity or associated conditions. Diminished renal function is the most important factor re quiring modification of recommended doses.

In deciding the dose of digoxin, several factors must be considered:

1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAU TIONS and Drug Interactions sections).

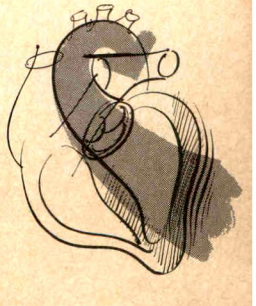
Consult complete product information before prescribing.

References: **1.** The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopr and digoxin in patients with mild to moderate heart failure. *JAMA*. 1988;259:539-544. **2.** DiBianco R, Shabetai Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in th treatment of patients with chronic heart failure. *N Engl J Med*. 1989;320:677-683. **3.** Guyatt GH, Sullivan MJJ, Falle EL, et al. A controlled trial of digoxin in congestive heart failure. *Am J Cardiol*. 1988;61:371-375. **4.** Gheorghiade M Hall V, Lakier JB, Goldstein S. Comparative hemodynamic and neurohormonal effects of intravenous captopril an digoxin and their combinations in patients with severe heart failure. *J Am Coll Cardiol*. 1989;13:134-142. **5.** Arnol SB, Byrd RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. *N Engl Med*. 1980;303:1443-1448. **6.** Alicandri C, Fariello R, Boni E, Zaninelli A, Muiesan G. Comparison of captopril an digoxin in mild to moderate heart failure. *Postgrad Med J*. 1986;62(suppl 1):170-175.

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a high-risk status for intracerebral hemorrhage in these patients; however, the overall balance of benefit and risk of thrombolysis in patient subgroups must still be assessed by large mortality trials.

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Early Prediction of Acute Myocardial Infarction from Clinical History, Examination and Electrocardiogram in the Emergency Room

Björn W. Karlson, Johan Herlitz, Olof Wiklund, Arina Richter, and Åke Hjalmarson

During a 21-month period, 7,157 patients came to our emergency room with chest pain or other symptoms suggestive of acute myocardial infarction (AMI), 4,690 were admitted to the hospital and 921 developed an AMI. Of the 1,576 patients admitted with a normal electrocardiogram, 90 (6%) developed an AMI. Of 1,964 patients with an abnormal electrocardiogram without signs of acute ischemia, 268 (14%) developed an AMI, and of 1,109 patients with acute ischemia on the electrocardiogram, 563 (51%) developed one. The patients were prospectively classified in the emergency room into 4 categories according to the degree of suspicion of AMI. Of 279 admitted and judged to have an obvious AMI, 245 (88%) developed an AMI; of 1,426 with a strong suspicion of AMI, 478 (34%) developed one; of 2,519 with a vague suspicion of AMI, 192 (8%) developed one; and of 466 with no suspicion of AMI, 6 (1%) developed one.

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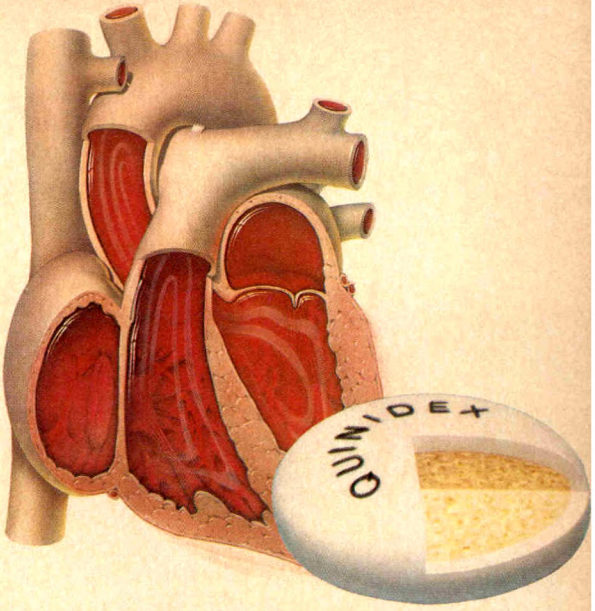
Usefulness of Severity of Myocardial Ischemia on Exercise Testing in Predicting the Severity of Myocardial Ischemia During Daily Activities

Jesaia Benhorin, Mady Moriel, Alex Gavish, Aharon Medina, Shmuel Banai, Michael Shapira, Shlomo Stern, and Dan Tzivoni

The relations between ischemic indexes on exercise testing and on ambulatory Holter recording were examined in 60 patients with stable coronary artery disease who exhibited an ischemic response on both testing procedures. Mean exercise test (Bruce protocol) duration was 7.4 ± 2.8 minutes and mean heart rate at 1-mm ST depression was 118 ± 20 beats/min. During 24-hour Holter recording the average number of ischemic episodes was 4.7 ± 2.6, the mean duration of daily ischemia was 62 ± 54 minutes and the mean heart rate at 1-mm ST depression was 93 ± 17 beats/min. The correlations between ischemic indexes on both testing procedures were generally very weak (mean $r^2 = 0.054$). However, the ischemic thresholds (heart rate at 1-mm ST depression) on both tests had a significant and probably meaningful correlation ($r^2 = 0.256$). These findings suggest that among selected patients with coronary artery disease, Holter recording might provide clinically relevant information in addition to that obtained by exercise testing.

Continued on page A22

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B.I.D.

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incompleteAV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital), phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

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Systemic Neurohumoral Activation and Vasoconstriction During Pacing-Induced Acute Myocardial Ischemia in Patients with Stable Angina Pectoris

Willem J. Remme, Peter W. de Leeuw, Marianne Bootsma, Maxime P. Look, and Dick A. C. M. Kruijssen

To test the hypothesis that myocardial ischemia may activate circulating catecholamines and the renin-angiotensin system, ischemia was induced by incremental atrial pacing in 25 patients with coronary artery disease, whereas 7 were not ischemic. During pacing, hemodynamic variables, regulating the myocardial supply-demand ratio, were comparable in ischemic and nonischemic patients, as was chest pain (78% [ischemic] and 72% [nonischemic]). Arterial neurohormones did not change in nonischemic patients, whereas dopamine levels remained unaltered in ischemic patients. In contrast, arterial norepinephrine and angiotensin II levels in ischemic patients increased by 76 and 50%, respectively, at maximal pacing rates and for several minutes after pacing, accompanied by an 11 and 13% increase in systemic resistance and arterial pressures, respectively. In contrast, arterial epinephrine only increased (50%) during maximal rates. Thus, myocardial ischemia activates circulating catecholamines and angiotensin II together with an increase in afterload, which suggests an (additional) antiischemic potential for agents modulating this neuroendocrine activation.

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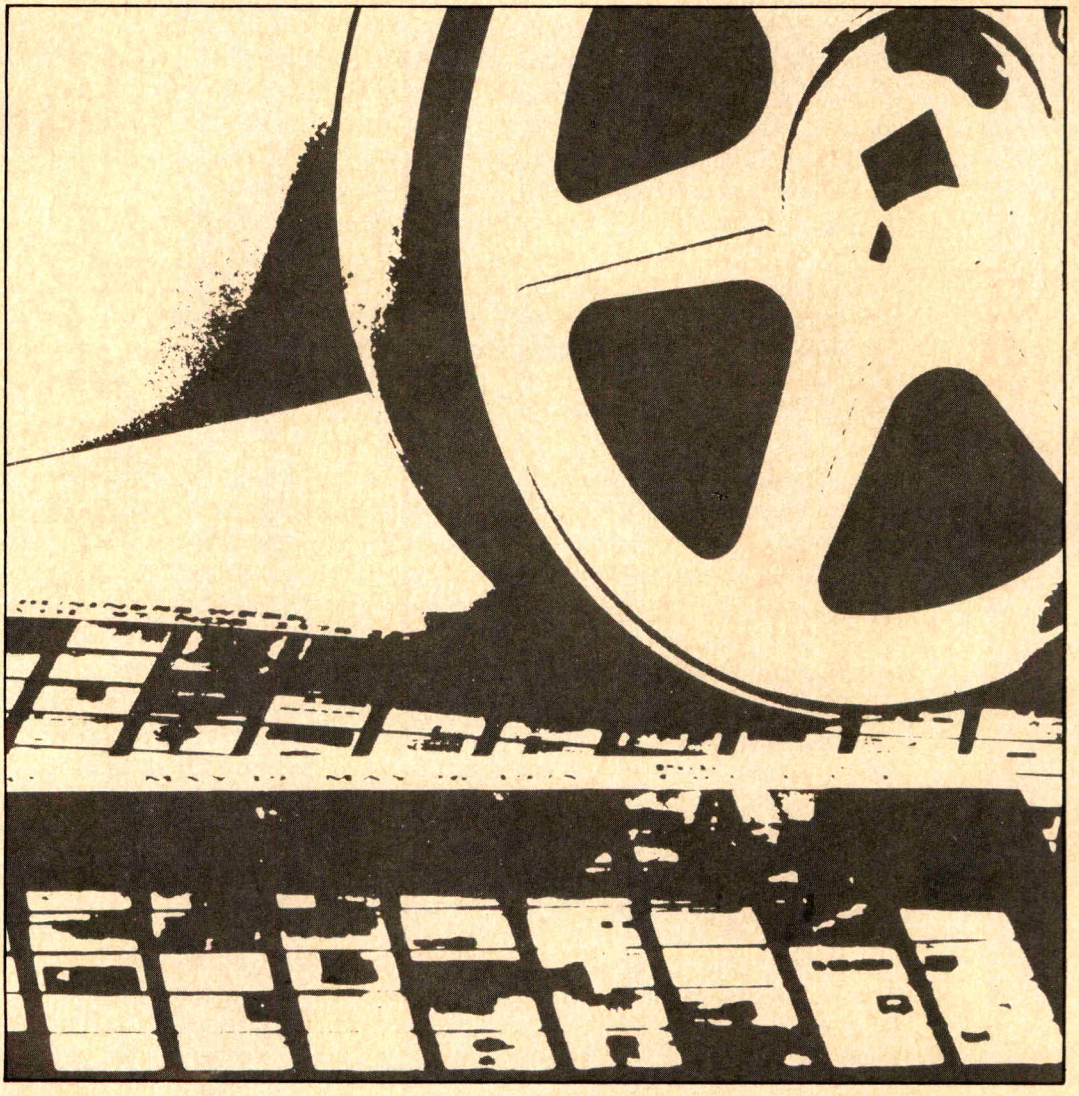
Frequency of Low Serum High-Density Lipoprotein Cholesterol Levels in Hospitalized Patients with "Desirable" Total Cholesterol Levels

Geoffrey S. Ginsburg, Charles Safran, and Richard C. Pasternak

The frequency of cholesterol levels <5.17 mmol/liter (200 mg/dl) and the prevalence of coronary artery disease (CAD) were determined from a cohort of 2,535 hospitalized patients. Forty-two percent (1,084 of 2,535) had serum cholesterol <5.17 mmol/liter and 690 of these 1,084 (64%) had CAD. Sixty percent (414 of 690) had high-density lipoprotein cholesterol (HDL) <0.90 mmol/liter (35 mg/dl). Furthermore, among patients undergoing angiography, approximately one-third had cholesterol levels <5.17 mmol/liter. A significant proportion of these had CAD (82%) and approximately 60% of them had HDL <0.90 mmol/liter (35 mg/dl). Therefore, serum cholesterol <5.17 mmol/liter is frequent among patients suspected of having established CAD. Other significant risk factors for CAD when cholesterol is <5.17 mmol/liter were: male gender and a family history of premature CAD. These data suggest that caution be used in applying National Cholesterol Education Program guidelines to hospitalized patients and that HDL measurement should be considered as part of an evaluation for CAD risk in men with a family history of premature CAD, even if the serum cholesterol level is <5.17 mmol/liter.

Continued on page A26

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Late Follow-Up After Repair of Left Ventricular Aneurysm and (Usually) Associated Coronary Bypass Grafting

Peter A. Baciewicz, William S. Weintraub, Ellis L. Jones, Joseph M. Craver, Caryn L. Cohen, Xudong Tao, and Robert A. Guyton

Long-term follow-up was obtained in 296 of 298 patients undergoing left ventricular aneurysm repair with or without coronary artery bypass grafting between 1974 and 1986 who were without recent myocardial infarction or other concurrent cardiac surgery. Ninety percent of the patients underwent concurrent bypass grafting, with an average of 2.2 ± 1.3 grafts placed. Fourteen patients (5%) died in the hospital, with most deaths attributable to left ventricular dysfunction. Advanced age and less extensive revascularization were correlates of in-hospital mortality. Advanced age, hypertension, left main coronary artery disease and emergent operative status were found to be predictors of long-term mortality.

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Seismocardiographic Changes Associated with Obstruction of Coronary Blood Flow During Balloon Angioplasty

David M. Salerno, John M. Zanetti, Lisa A. Green, Michael R. Mooney, James D. Madison, and Robert A. Van Tassel

Seismocardiography, a new noninvasive technique, detects low-frequency cardiac vibrations on the chest wall during ventricular contraction and during both early and late ventricular filling. Seismocardiograms and electrocardiograms were recorded sequentially during percutaneous transluminal coronary angioplasty in 35 patients. For comparison, sequential seismocardiograms were also obtained from 15 healthy volunteers. Electrocardiograms were blindly scored for ST change from baseline (0 = none, 1 = 0.5 mm ST depression, 2 = ≥1.0 mm ST depression, 3 = ST elevation). Seismocardiograms were blindly scored for change from baseline (0 = none, 1 = mild, 2 = moderate, 3 = marked) for both the systolic and diastolic waves. The average maximal systolic seismocardiographic score was 2.5 ± 0.8 for angioplasty patients and 1.0 ± 0.9 for volunteers ($p < 0.001$). The average maximal diastolic seismocardiographic score was 2.3 ± 0.8 for angioplasty patients and 0.7 ± 0.9 for volunteers ($p < 0.001$). Both electrocardiograms and seismocardiograms changed rapidly during percutaneous transluminal coronary angioplasty, whereas seismocardiograms did not change in volunteers. Most changes developed when the catheter crossed the lesion, before balloon inflation. These findings are consistent with the hypothesis that the seismocardiographic changes are due to ischemic changes in ventricular wall motion or compliance. Seismocardiographic changes persisted longer than electrocardiographic changes, possibly due to delayed recovery in ventricular function after ischemia.

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Epicardial Mapping in Patients with "Nodoventricular" Accessory Pathways

Challon J. Murdock, James W. Leitch, George J. Klein, Gerard M. Guiraudon, Raymond Yee, and Wee Siong Teo

Patients with electrophysiologic features suggesting nodoventricular fibers usually have right parietal atrioventricular accessory pathways with decremental conduction properties. The experience with 11 patients who had clinical and electrophysiologic features consistent with a nodoventricular pathway and who underwent operative correction was reviewed. Epicardial mapping demonstrated a right atrioventricular pathway with decremental properties mimicking a nodoventricular pathway in all patients. The earliest site of ventricular activation during maximal preexcitation was the midanterior right ventricle, consistent with insertion of these pathways into the right bundle branch system in 7 patients. In the remaining 4 patients, it was at the atrioventricular groove, as for typical Wolff-Parkinson-White syndrome.

VALVULAR HEART DISEASE

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Time-Motion Reconstruction of Mitral Leaflet Motion from Two-Dimensional Echocardiography in Mitral Valve Prolapse

Riccardo Pini, Barbara Greppi, Mary J. Roman, Randi Kramer-Fox, and Richard B. Devereux

To verify that posterior motion of mitral leaflets recognized as mitral valve prolapse (MVP) by M-mode echocardiography could represent either mitral leaflet billowing into the left atrium or exaggerated dynamic expansion of the mitral anulus, computerized time-motion reconstruction was derived from the anteroposterior displacement of mitral valve leaflets from 2-dimensional echocardiograms. Late or holosystolic posterior displacement of mitral leaflets occurred in time-motion reconstructions from 24 of 24 MVP patients (100%) with and 20 of 24 MVP patients (83%) without leaflet billowing compared with 4 of 35 (11%) age-sex matched normal adults ($p < 0.0000002$). When the mitral leaflet movements were reconstructed using the posterior end of the mitral anulus as the reference point, posterior leaflet displacement was significantly decreased ($p < 0.02$) in patients with nonbillowing MVP, but not in 20 of 24 patients with leaflet billowing. Thus, M-mode appearance of MVP reflects the effects of distinct abnormalities of mitral anular and leaflet dynamics.

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EMINASE®
ANISTREPLASE 30 U

INDICATIONS AND USAGE: EMINASE® ANISTREPLASE, is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms **(see CLINICAL PHARMACOLOGY).**

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, EMINASE® is contraindicated in the following situations: ■ active internal bleeding ■ history of cerebrovascular accident ■ recent (within 2 months) intracranial or intraspinal surgery or trauma **(see WARNINGS)** ■ intracranial neoplasm, arteriovenous malformation, or aneurysm ■ known bleeding diathesis ■ severe, uncontrolled hypertension. EMINASE® should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

WARNINGS: Bleeding: (See ADVERSE REACTIONS) The most common complication associated with EMINASE® therapy is bleeding. The types of bleeding associated with thrombolytic therapy can be divided into two broad categories: 1. Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal, ocular, or intracranial sites. 2. Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of EMINASE® had dissipated, but while heparin therapy was continuing. As fibrin is lysed during EMINASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with EMINASE®. Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary following administration of EMINASE®, it is preferable to use an upper-extremity vessel that is accessible to manual compression. A pressure dressing should be applied, and the puncture site should be checked frequently for evidence of bleeding. Each patient being considered for therapy with EMINASE® should be carefully evaluated and anticipated benefits should be weighed against potential risks associated with therapy. In the following conditions, the risks of EMINASE® therapy may be increased and should be weighed against the anticipated benefits: ■ recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels) ■ cerebrovascular disease ■ recent gastrointestinal or genitourinary bleeding (within 10 days) ■ recent trauma (within 10 days) including cardiopulmonary resuscitation ■ hypertension: systolic BP $\geq$180 mmHg and/or diastolic BP $\geq$110 mmHg ■ high likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation) ■ subacute bacterial endocarditis ■ acute pericarditis ■ hemostatic defects including those secondary to severe hepatic or renal disease ■ pregnancy ■ age >75 years (Use of EMINASE® in patients over 75 years old has not been adequately studied.) ■ diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ septic thrombophlebitis or occluded AV cannula at seriously infected site ■ patients currently receiving oral anticoagulants (e.g., warfarin sodium) ■ any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when injections of EMINASE® are administered.

Hypotension: Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis, has occasionally been observed soon after intravenous EMINASE® administration. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate symptomatic treatment should be administered.

PRECAUTIONS: General: Standard management of myocardial infarction should be implemented concomitantly with EMINASE® treatment. Invasive procedures should be minimized **(see WARNINGS).** Anaphylactoid reactions have rarely been reported in patients who received EMINASE®. Accordingly, adequate treatment provisions such as epinephrine should be available for immediate use.

Readministration: Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE® may not be as effective if administered more than 5 days after prior EMINASE® or Streptokinase therapy or streptococcal infection, particularly between 5 days and 6 months. Increased antistreptokinase antibody levels between 5 days and 6 months after EMINASE® or Streptokinase administration may also increase the risk of allergic reactions. Repeated administration of EMINASE® within one week of the initial dose has occurred in a small number of patients treated for AMI and non-AMI conditions. The incidence of hematomas/bruising was somewhat greater in those patients who received repeat doses of EMINASE® but otherwise the adverse event profile was similar to those who received one dose.

Laboratory Tests: Intravenous administration of EMINASE® will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). Results of coagulation tests and/or measures of fibrinolytic activity performed during EMINASE® therapy may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. EMINASE®, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (2000 to 3000 KIU/mL) can, to some extent, mitigate this phenomenon.

Drug Interactions: The interaction of EMINASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin and dipyridamole) may increase the risk of bleeding if administered prior to EMINASE® therapy.

Use of Anticoagulants: EMINASE® alone or in combination with antiplatelet agents and anticoagulants may cause bleeding complications. Therefore, careful monitoring is advised, especially at arterial puncture sites. In clinical studies, a majority of patients treated received anticoagulant therapy postdosing with EMINASE® during their hospital stay and a minority received heparin pretreatment with EMINASE®. The use of antiplatelet agents increased the incidence of bleeding events similarly in patients treated with EMINASE® or nonthrombolytic therapy. There was no evidence of a synergistic effect of combined EMINASE® and antiplatelet agents on bleeding events. In addition, there was no difference in the incidence of hemorrhagic CVA's in EMINASE® treated patients who did or did not receive aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Studies to determine mutagenicity and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested.

Pregnancy (Category C): Animal reproduction studies have not been conducted with EMINASE®. It is also not known whether EMINASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EMINASE® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether EMINASE® is excreted in human milk. Because many drugs are excreted in human milk, the physician should decide whether the patient should discontinue nursing or not receive EMINASE®.

Pediatric Use: Safety and effectiveness of EMINASE® in children have not been established.

ADVERSE REACTIONS: Bleeding: The incidence of bleeding (major or minor) varied widely from study to study and may depend on the use of arterial catheterization and other invasive procedures, patient population, and/or concomitant therapy. The overall incidence of bleeding in patients treated with EMINASE® in clinical trials (n=5275) was 14.6%, with nonpuncture-site bleeding occurring in 10.2%, and puncture-site bleeding occurring in 5.7%, of these patients. Bleeding at the puncture site occurred more frequently in clinical trials in which the patients underwent immediate coronary catheterization (13.3%, n=637) compared with those who did not (3.0%, n=2023). The incidence of presumed intracranial bleeding within 7 days postdosing with EMINASE® was 0.57% (n=5275; 0.34% etiology confirmed hemorrhagic; 0.23% etiology not confirmed) compared to 0.16% (n=1249) after nonthrombolytic therapy. In the AIMS trial the overall incidence of bleeding in patients treated with EMINASE® was 14.8% compared with 3.8% for placebo. The incidence of specific bleeding events was:

Type of Bleeding	EMINASE® (n=500)	Placebo (n=501)
Puncture site	4.6%	<1%
Nonpuncture site hematoma	2.8%	<1%
Hematuria/Genitourinary	2.4%	<1%
Hemoptysis	2.2%	<1%
Gastrointestinal hemorrhage	2.0%	1.4%
Intracranial	1.0%	<1%
Gum/Mouth Hemorrhage	1.0%	0
Epistaxis	<1%	<1%
Anemia	<1%	<1%
Eye Hemorrhage	<1%	<1%
Hemorrhage (unspecified)	<1%	0

In this study there was no difference between EMINASE® and placebo in the incidence of major bleeding events. Should serious bleeding (not controlled by local pressure) occur in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), any concomitant heparin should be terminated immediately and the administration of protamine to reverse heparinization should be considered. If necessary, the bleeding tendency can be reversed with appropriate replacement therapy. Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding **(see WARNINGS).**

Cardiovascular: The most frequently reported adverse experiences in EMINASE® clinical trials (n=5275) were arrhythmia/conduction disorders which were reported in 38% of patients treated with EMINASE® and 46% of nonthrombolytic control patients. Hypotension occurred in 10.4% of patients treated with EMINASE® compared to 7.9% for patients who received nonthrombolytic treatment **(see WARNINGS).**

Allergic-type Reactions: Anaphylactic and anaphylactoid reactions have been observed rarely (0.2%) in patients treated with EMINASE® and are similar in incidence to Streptokinase (0.1% anaphylactic shock in one study). These included symptoms such as bronchospasm or angioedema. Other milder or delayed effects such as urticaria, itching, flushing, rashes, and eosinophilia have been occasionally observed. A delayed purpuric rash appearing one to two weeks after treatment has been reported in 0.3% of patients. The rash may also be associated with arthralgia, ankle edema, gastrointestinal symptoms, mild hematuria, and mild proteinuria. This syndrome was self-limiting and without long-term sequelae.

Risk of Viral Transmission: Six batches of EMINASE® (five different batches of Lys-Plasminogen) were used in clinical trials designed specifically to monitor possible hepatitis non-A, non-B transmission. No case of hepatitis was diagnosed in patients receiving EMINASE®. Lys-Plasminogen is derived from human plasma obtained from FDA approved sources and tested for absence of viral contamination, including human immunodeficiency virus type-1 (HIV-1) and hepatitis B surface antigen. The manufacturing process includes a vapor-heat treatment step for inactivation of viruses. The entire manufacturing process has also been validated to yield a cumulative reduction of $\geq 10^{21}$ fold HIV-1 infectious particles, i.e., $\geq 10^{6}$ infectious particles removed by vapor-heat treatment and a cumulative total of $\geq 10^{15}$ infectious particles removed by the various steps in the purification process.

Causal Relationship Unknown: Since the following experiences may also be associated with AMI or other therapy, the causal relationship to EMINASE® administration is unknown. The following adverse experiences were infrequently (<10%) reported in clinical trials: **Body as a Whole**—chills, fever, headache, shock; **Cardiovascular**—cardiac rupture, chest pain, emboli; **Dermatology**—purpura, sweating; **Gastrointestinal**—nausea and/or vomiting; **Hemic and Lymphatic**—thrombocytopenia; **Metabolic and Nutritional**—elevated transaminase levels; **Musculoskeletal**—arthralgia; **Nervous**—agitation, dizziness, paresthesia, tremor, vertigo; **Respiratory**—dyspnea, lung edema.

DOSAGE AND ADMINISTRATION: Administer EMINASE® as soon as possible after the onset of symptoms. The recommended dose is 30 units of EMINASE® administered only by intravenous injection over 2 to 5 minutes into an intravenous line or vein.

Reconstitution: 1. Slowly add 5 mL of Sterile Water for Injection, U.S.P., by directing the stream of fluid against the side of the vial. 2. Gently roll the vial, mixing the dry powder and fluid. **Do not shake.** Try to minimize foaming. 3. The reconstituted preparation is a colorless to pale yellow transparent solution. Before administration, the product should be visually inspected for particulate matter and discoloration. 4. Withdraw the entire contents of the vial. 5. The reconstituted solution should not be further diluted before administration or added to any infusion fluids. No other medications should be added to the vial or syringe containing EMINASE®. 6. If EMINASE® is not administered within 30 minutes of reconstitution, it should be discarded.

HOW SUPPLIED: EMINASE® is supplied as a sterile, lyophilized powder in 30-unit vials. NDC 57294-030-20.

Storage: Store lyophilized EMINASE® between 2-8°C (36-46°F). Do not use beyond the expiration date printed on the vial.

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Radiation Exposure of Pediatric Patients and Physicians During Cardiac Catheterization and Balloon Pulmonary Valvuloplasty
Jiunn-Ren Wu, Teh-Yang Huang, Ding-Kwo Wu, Pin-Chieh Hsu, and Pao-Shan Weng

To evaluate radiation exposure of various areas of the body, thermoluminescent dosimeters were applied to 61 pediatric patients and personnel during catheterization, and 4 patients during balloon pulmonary valvuloplasty. Average skin dose to the chest is 121 μGy during chest posteroanterior roentgenography, 5,182 μGy during catheterization and 641 mGy during balloon pulmonary valvuloplasty. The exposure of personnel is relatively small, but the exposure to the skin of right lateral chest area of patients undergoing valvuloplasty is extremely high, perhaps as high as the equivalent of 1,000 chest x-rays.

MISCELLANEOUS

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Role of Angioscopy in the Treatment of Peripheral Vascular Disease with Percutaneous Atherectomy
Gerhard Bauriedel, Samuel J. De Maio, Jr., and Berthold Höfling

The role of adjunctive video angioscopy was evaluated in 43 patients with 57 lesions (superficial femoral [n = 46], popliteal [n = 11]) with symptomatic peripheral vascular disease undergoing percutaneous atherectomy with the Simpson atherocath. Thirty-three lesions were stenotic (85.7 to 10.8%) and 24 were totally occluded (0.5 to 10.6 cm in length). Intraluminal inspection with angioscopy could be performed in 55 of 57 lesions (96%) before and in 39 of these 55 (71%) after atherectomy. Failure in adequate imaging was usually attributed to insufficient irrigation. Angioscopic passage revealed that often long total occlusions, as determined by angiography, consisted of $\geq$1 discrete occlusion with interposed patent thrombus-free vascular segments. After atherectomy, in 15 instances with an acceptable angiographic result, angioscopy was helpful in identifying residual plaques and flaps which were then selectively atherectomized. In conclusion, angioscopy is a useful adjunct to angiography in optimizing vascular recanalization with percutaneous atherectomy.

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Evolution of Heart Rate Responsiveness After Orthotopic Cardiac Transplantation
Laszlo Rudas, Peter W. Pflugfelder, Alan H. Menkis, Richard J. Novick, F. Neil McKenzie, and William J. Kostuk

Heart changes in response to orthostasis and treadmill exercise were studied in 52 orthotopic cardiac transplant recipients grouped according to time after transplantation. Patients late after transplantation showed significant cardioacceleration within 10 cardiac cycles after standing to a maximum of 10.7 $\pm$ 4.9 beats at 2 minutes. During exercise, heart rate increased more rapidly during the first minute in the same patients and

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decreased rapidly after exercise in contrast to patients early after transplantation in whom heart rate continued to increase. Heart rate responsiveness evolves with time after orthotopic heart transplantation, possibly through the emergence of intrinsic cardiac autoregulation.

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Preserved Atrial Natriuretic Peptide Secretory Function After Cardiac Transplantation

Randall C. Starling, Thomas M. O'Dorisio, William B. Malarkey, Kevin D. Murray, P. David Myerowitz, and Robert J. Cody

The purpose of this investigation was to determine whether atrial natriuretic peptide (ANP) secretory function is preserved after cardiac transplantation. Exercise was used as a provocative physiologic stimulus. Thirteen hemodynamically stable orthotopic cardiac transplant recipients performed supine exercise on a bicycle. Right atrial pressure increased 2.2-fold (6 ± 1 to 13 ± 2 mm Hg), and pulmonary artery wedge pressure increased 2.1-fold (11 ± 1 to 23 ± 7 mm Hg) with exercise. Resting ANP level was 114 ± 19 pg/ml and at peak exercise increased to 373 ± 61 pg/ml, a 4.3-fold increase. A correlation between venous ANP levels and hemodynamics (right atrial pressure) was observed ($r = 0.49$ $p = 0.01$). It is concluded that resting ANP levels are elevated after cardiac transplant, the levels correlate with the intracardiac hemodynamics, and exercise-induced augmentation of plasma levels occurs.

METHODS

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Ability of High-Intensity Ultrasound to Ablate Human Atherosclerotic Plaques and Minimize Debris Size

Alexander Ernst, Eric A. Schenk, Sheryl M. Gracewski, Timothy J. Woodlock, Francis G. Murant, Howard Alliger, and Richard S. Meltzer

To investigate whether ultrasound can destroy atherosclerotic plaques while sparing the normal arterial wall, 279 normal human aortic sites and 119 fibrous and 193 calcified plaques were ultrasonically irradiated in a water tank at 20 kHz and at 5 different power intensities. At high power levels, no significant difference was found in perforation times between normal aortic sites and fibrous and calcified plaques. At lowest power, perforation time for normal aortic wall was significantly longer than for fibrous and calcified plaques: 30 ± 18, 14 ± 7 ($p < 0.001$), and 12 ± 8 seconds ($p < 0.001$), respectively. Mean debris particle diameter was 7.0 ± 4.8 μm. Thus, at certain power intensities ultrasound may selectively ablate human atherosclerotic plaques compared with normal arterial wall.

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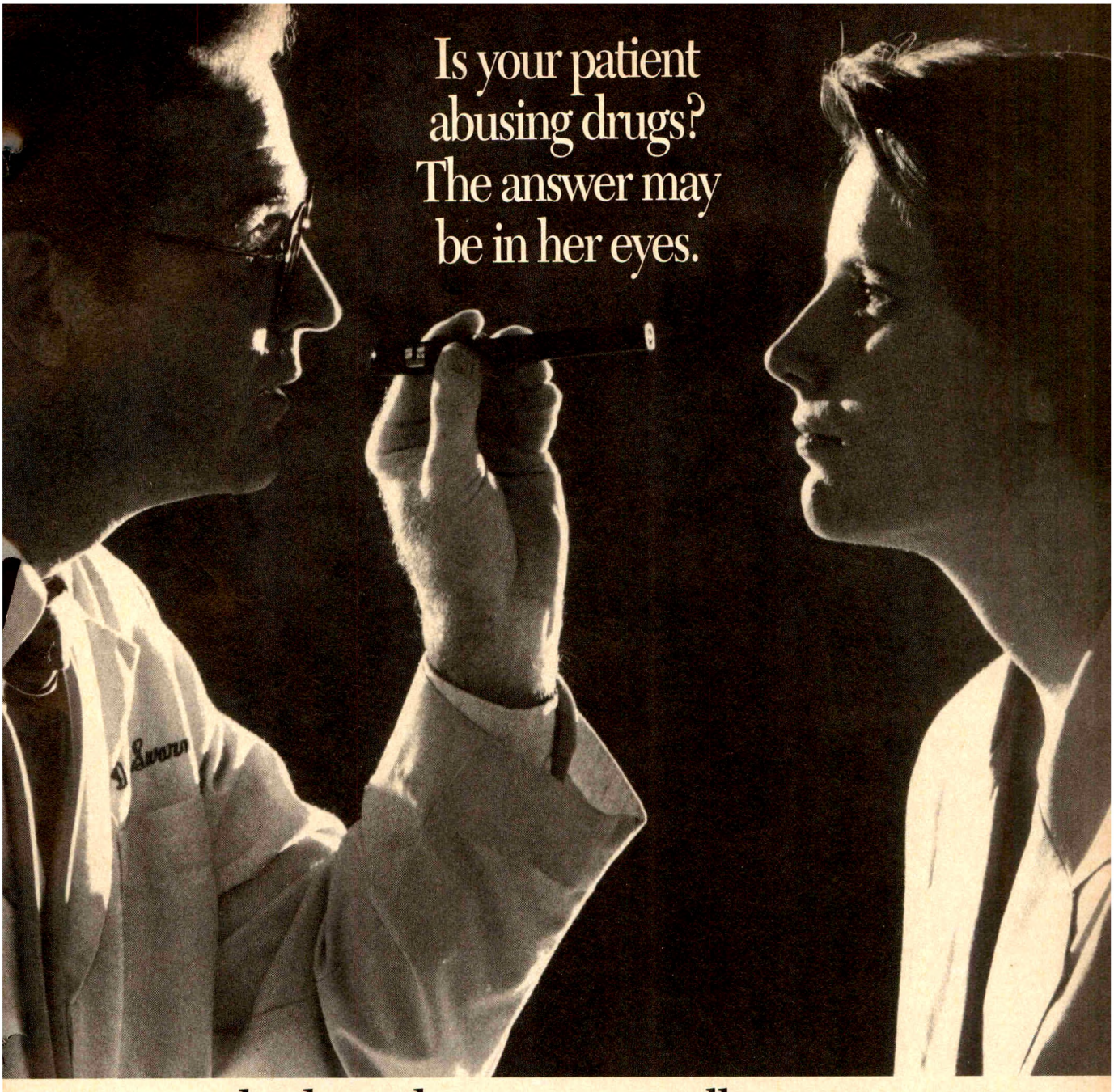
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Pupil size	Dilation; Constriction
Pupil reaction	Slow, sluggish, or absent response
Nystagmus	Failure to hold gaze; Jerkiness of movements
Convergence	Inability to track or hold the cross-eyed position
Corneal reflex	Decreased rate of blinking

Tennant F. The rapid eye test to detect drug abuse. *Postgrad Med.* 1988;84:109-114.

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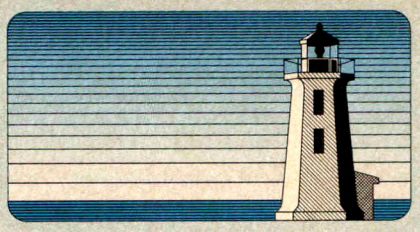
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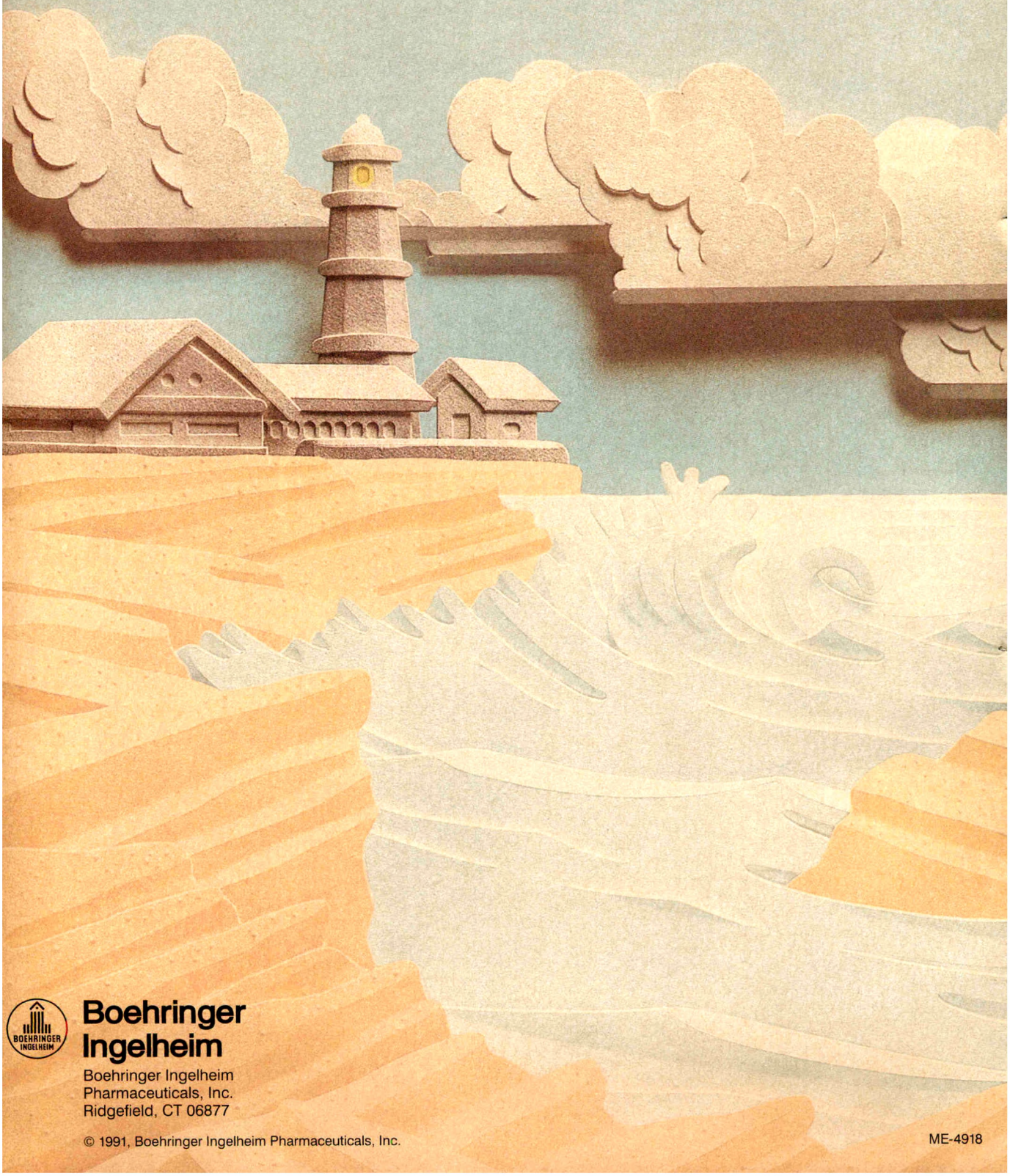
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Outcome of Patients Who Were Admitted to a New Short-Stay Unit to "Rule-Out" Myocardial Infarction

Jean-Michel Gaspoz, MD, Thomas H. Lee, MD, E. Francis Cook, ScD, Monica C. Weisberg, RN, and Lee Goldman, MD

For emergency room patients with a low probability of acute myocardial infarction, we established a new short-stay coronary observation unit, a 2-bed nonintensive care unit with telemetry monitoring adjacent to the emergency room. Of 512 consecutive admissions to the coronary observation unit, 425 (83%) were discharged home without evidence of acute myocardial infarction or serious complications (mean length of stay, 1.2 days; median length of stay, 1 day); 87 (17%) were transferred to other hospital beds. The rate of acute myocardial infarction was 3%. No deaths and only 1 serious complication occurred in the coronary observation unit. At 6 month follow-up, the cardiac survival rate was 99% for patients sent home directly from this unit.

It is concluded that the coronary observation unit is safe and adequate for ruling out acute myocardial infarction in a defined subset of patients. Short-stay units, however, encourage early discharges which, when premature, may miss patients who are at risk of having complications shortly thereafter. Strategies such as mandatory but expeditious predischarge stress testing to encourage early but not premature discharge may augment the efficiency of coronary observation units.

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Patients who are admitted to "rule-out myocardial infarction" account for up to 70% of coronary care unit admissions and a large proportion of the unit's charges.[1–3] One approach to reduce costs is to develop algorithms to decrease unnecessary admissions.[4–8] Another approach is to develop cost-effective alternatives to coronary care units for patients with low to moderate probabilities of myocardial infarction.[9,10] The present study evaluated a new short-stay coronary observation unit for patients with possible cardiac ischemic pain and a low probability of myocardial infarction.

METHODS

From its inception on April 6, 1986, through November 30, 1988, 512 patients with suspected cardiac ischemic pain were admitted to the coronary observation unit at Brigham and Women's Hospital, a 720-bed teaching hospital in Boston.

Characteristics of the coronary observation unit: The coronary observation unit consists of 2 beds with telemetry monitoring within a 10-bed holding unit adjacent to the emergency room. The holding unit is used for patients with expected hospitalizations of ≤72 hours, i.e., asthma or pyelonephritis, but is not generally used as a "holding area" while waiting for a bed to be available in the hospital. The nurse:patient ratio is 1:5, which is similar to the nursing intensity of the general medical floors. At least 1 nurse experienced in the interpretation of cardiac monitor tracings is always physically present in the holding unit, and housestaff

TABLE I Clinical Characteristics of the 512 Admissions to the Coronary Observation Unit (n = 512)

		No. (%)
Male gender		247 (48%)
Age (yr) (mean ± SD)		59 ± 15
Chief complaint:		
Chest pain		488 (95%)
Arm, neck, epigastric pain		24 (5%)
Among those with chest pain	(n = 488)	
Chest pain of substernal location	354 (73%)	
Quality of chest pain		
Pressure	312 (64%)	
Sharp	51(10%)	
Other	125 (26%)	
Chest pain reproduced by		
Deep breathing	28 (6%)	
Palpation	40 (8%)	
Position	20 (4%)	
Time since onset of suspected cardiac ischemic pain		
≤4 hours		223 (45%)
4–12 hours		115 (23%)
>12 hours		162 (32%)
Duration of longest episode of pain		
≤60 minutes		231 (51%)
>60 minutes		223 (49%)
History of angina or myocardial infarction		224 (44%)
Associated symptoms		
Diaphoresis		137 (27%)
Dyspnea		210 (41%)
Dizziness		58 (11%)
Physical examination: > bibasilar rales		71 (14%)
Emergency room electrocardiogram		
Changes consistent with ischemia or infarction not known to be old		84 (16%)
Changes consistent with ischemia or infarction known to be old		73 (14%)
Other old or new abnormalities		97 (19%)
Nonspecific ST-T-wave changes		161 (32%)
Normal		97 (19%)

Missing data: time since onset of pain, 12 observations; duration of longest episode of pain, 58 observations.
SD = standard deviation.

coverage is provided by residents in the adjacent emergency room.

Eligibility: The following admission guidelines were set: (1) a probability of acute myocardial infarction ≤10% as determined by our clinical algorithm[4,5]; (2) an anticipated stay of ≤48 hours; and (3) the absence of signs of acute ischemia or infarction on the emergency room electrocardiogram, ventricular couplets or bigeminy, paroxysmal supraventricular tachycardia or arrhythmias requiring intravenous treatment, second- or third-degree atrioventricular block or new bundle branch block, persistent or recurrent ischemic pain after initial treatment in the emergency room or need for intravenous nitroglycerin, systolic blood pressure >200 or <100 mm Hg, diastolic blood pressure >120 mm Hg, congestive heart failure, or conditions requiring intravenous medication or requiring more than the available level of nursing care.

Admission and disposition protocols: All patients had electrocardiograms recorded every 12 hours and a sampling of serum creatine kinase and its isoenzyme MB on admission and every 8 hours for up to 24 hours. Patients were transferred to an appropriate hospital setting if they ruled-in for a myocardial infarction, or developed complications that would have made them ineligible for initial admission to the coronary observation unit. If none of these occurred, patients were discharged home after about 24 hours, and appropriate ambulation or formal exercise stress testing, or both, was performed, unless their private internist or cardiologist or the senior staff internist in charge of the unit transferred the patient to another hospital setting for further evaluation. Formal cardiology consultation was optional.

Data collection: Data collected prospectively from the emergency room evaluation have been described in detail elsewhere.[4,5,10,11] Data from the hospitalization included clinical course, cardiac enzymes, and dates and times of complications and procedures.

Six-month follow-up data were collected for all clinical events, tests, hospitalizations and subsequent diagnoses for the 488 patients who accounted for the 512 admissions. Six-month follow-up was obtained in 98% of the patients through phone contact with the patients or their next of kin, medical record review, a letter to the patient's last known address, or contact with the patient's last known physician. For the other 2%, the records of the Massachusetts Bureau of Vital Statistics were reviewed.

A final diagnosis of myocardial infarction was made based on standard enzymatic or electrocardiographic criteria described in detail elsewhere,[4,5,10,11] or on death from sudden cardiac arrest within 72 hours of presentation in a patient in whom no other cause of death was suspected and in whom the course was consistent with an acute myocardial infarction. The diagnosis of acute ischemic heart disease without infarction was made if myocardial infarction was not diagnosed and if 2 additional criteria were met. The first was that the diagnosis of angina was made by the senior clinician associated with the case and was not contraindicated by follow-up information in the hospital, or that it was based on a positive exercise test result, a positive coronary angiographic result or the hospital course. The second was that the patient's chest pain was either new or worse (in frequency, severity or duration) than any previous chronic angina, regardless of whether the new or worsening pain was precipitated by heart failure, arrhythmias or other conditions.

RESULTS

Of the 512 admissions for suspected cardiac ischemic pain, 488 (95%) had a chief complaint of chest pain (Table I). In the patients with chest pain, the pain

was substernal in 73%, had a pressure-like character in 64%, and usually was not reproduced by deep breathing, palpation or changes in position. However, emergency room electrocardiograms were relatively benign. Of the 84 electrocardiograms (16%) that were consistent with ischemia or infarction not known to be old, 77 (92%) were ST-segment depressions of <1 mm or T-wave inversions consistent with strain as well as ischemia. Thus, the electrocardiographic guidelines for eligibility were generally well followed.

Acute myocardial infarction was diagnosed in 15 admissions (3%), including 11 on the basis of enzymatic or electrocardiographic criteria in the coronary observation unit in ≤24 hours and 1 who left against medical advice but returned 48 hours later with enzymatic and electrocardiographic criteria. Two patients had recurrent chest pain and were transferred in ≤48 hours to the coronary care unit and to a stepdown unit where acute myocardial infarction was diagnosed by enzymatic criteria. One additional patient met our criteria for acute myocardial infarction by developing sudden complete heart block with a junctional escape rhythm and cardiogenic shock after 24 hours in the coronary observation unit; she was transferred to the coronary care unit where, despite adequate treatment, she died 4 hours later from cardiac arrest. Acute ischemic heart disease without infarction was diagnosed in 143 admissions (28%), whereas an additional 39 (8%) were assigned another cardiac diagnosis and 315 (61%) a noncardiac diagnosis.

All 3 in-hospital deaths were cardiac and occurred in the coronary care unit. In addition to the patient previously mentioned, 1 additional patient with acute myocardial infarction diagnosed ≤24 hours after admission died from cardiac arrest 4 days after transfer from the coronary observation unit, whereas another 81-year-old patient died 3 weeks after transfer from complications including arrhythmias and heart failure.

Complications were few. Overall, 2 admissions (0.4%) had cardiac arrest, 1 each (0.2%) developed cardiogenic shock and complete heart block, 18 (3.5%) had recurrent ischemic pain after leaving the emergency room, and 2 (0.4%) had congestive heart failure.

Patients discharged directly from the coronary observation unit: After a mean length of stay of 1.2 ± 0.55 days and a median length of stay of 1 day, 425 (83%) patients were discharged home directly from the coronary observation unit (Table II). Of these 425 patients, only 1, who left against medical advice, had an acute myocardial infarction. Another 104 patients (24%) had acute ischemic heart disease without infarction. Eighty-nine (86%) of these 104 patients either had normal admission electrocardiograms or had only old or nonspecific abnormalities. One 92-year-old patient had an admission electrocardiogram showing questionable transient anterior ST elevations as well as lateral T-wave inversions, whereas 14 others (13%) had ST or T-wave changes consistent with ischemia or strain that were not known to be old. Only 1 of these 104 patients had an episode of recurrent chest pain while in the coronary observation unit; the pain was not accompanied by electrocardiographic changes and the patient was discharged on medical treatment after performing a standard Bruce protocol exercise test for >9 minutes.

TABLE II Disposition from the Coronary Observation Unit (n = 512)

		No. (%)
Patients discharged home directly from the coronary observation unit		425 (83%)
Length of stay in days		
Mean ± SD	1.2 ± 0.55	
Median	1	
Maximum/minimum	4/0	
Final diagnoses	(n = 425)	
Myocardial infarction	1 (0.25%)*	
Acute ischemic heart disease without infarction	104 (24%)	
Other cardiac	30 (7%)	
Other noncardiac	290 (68%)	
Patients transferred to other hospital beds		87 (17%)
Length of stay in days		
Mean ± SD	7.9 ± 8.4	
Median	5	
Maximum/minimum	52/1	
Final diagnoses	(n = 87)	
Myocardial infarction	14 (16%)	
Acute ischemic heart disease without infarction	39 (45%)	
Other cardiac	9 (10%)	
Other noncardiac	25 (29%)	

*Left against medical advice.
SD = standard deviation.

Patients transferred to other levels of care: Of the 87 other patients (17%) who were transferred to other hospital beds, 21 (24%) went to the coronary care unit, 36 (41%) to a stepdown unit and 30 (35%) to the wards. Some patients had >1 reason for transfer, which was primarily prompted by: heart block (1 patient), diagnosed acute myocardial infarction (11 patients), recurrence of presumed cardiac ischemic pain (12 patients), development of congestive heart failure (1 patient), supraventricular tachy- or bradyarrhythmias (13 patients), new first- or second-degree atrioventricular block (2 patients), a worrisome pattern of ischemic pain responsible for the emergency room visit (32 patients), other cardiac diseases such as pericarditis or digitalis intoxication (4 patients), and other noncardiac diseases such as pulmonary embolism or cellulitis (11 patients). As expected, the final diagnoses of acute myocardial infarction and of acute ischemic heart disease without infarction were higher among patients

TABLE III Clinical Outcomes of Patients at Six Months after Being Discharged Alive

	No.	Fatal AMI (%)	Nonfatal AMI (%)	Cardiac Survival (%)
Disposition*				
Discharged home directly from the coronary observation unit	406	1 (0.2)	6 (1.5)	99
Transferred to other hospital beds	79	1 (1.3)	0 (0)	97.5
Diagnosis†				
Acute myocardial infarction	13	0 (0)	0 (0)	100
Acute ischemic heart disease	133	0 (0)	2 (1.5)	100
Other cardiac diagnoses	34	1 (2.9)	0 (0)	97
Other noncardiac diagnoses	305	1 (0.4)	4 (1.3)	98
Total	485	2 (0.4)	6 (1.2)	98.8

*The number of patients differs from Table II because 3 patients died in the hospital, and 5 other transferred patients and 19 patients discharged from the coronary observation unit were admitted twice.
†The number of patients differs from Table II because 2 patients with acute myocardial infarction and 1 with another cardiac diagnosis died in the hospital; 10 patients with acute ischemic heart disease, 4 with other cardiac diagnoses, and 10 with other noncardiac diagnoses were admitted twice.
AMI = acute myocardial infarction.

who were transferred, and their mean and median lengths of stay were longer (Table II).

Of the 39 admissions with a diagnosis of acute ischemic heart disease without infarction who were kept in the hospital and transferred to other settings, 11 (28%) had admission electrocardiograms showing ST and T-wave changes consistent with ischemia or strain, whereas the 28 others (72%) had abnormalities that were either old, or nonspecific, or had normal electrocardiograms; 10 (26%) had had recurrent ischemic pain while in the coronary observation unit, and 1 (2.6%) developed congestive heart failure.

Six-month follow-up: Six months after presentation, 8 additional patients (1.6%) had an acute myocardial infarction and 11 additional patients died, including 6 from cardiac causes, yielding a cardiac survival rate at 6 months of 98.8% (Table III). Among the 406 patients discharged home directly from the coronary observation unit, 8 deaths occurred within 6 months of discharge, 4 of which were cardiac (cardiac survival rate at 6 months, 99%). Of the 7 myocardial infarctions (1.7%), 2 occurred at 4.5 months, 1 of which was fatal, and 5 occurred within 3 days of discharge and represented 1.2% of this group of patients. There were 6 myocardial infarctions during follow-up among the 311 patients discharged after a stay of ≤24 hours, and 1 myocardial infarction among the 95 patients who stayed longer (Kaplan-Meier probabilities of 0.0196 and 0.0105, respectively; log-rank test, $p = 0.55$).

All 5 myocardial infarctions within 72 hours of discharge occurred among the 311 patients with a length of stay of ≤24 hours. Of these 5 patients, 2 had discharge diagnoses of acute ischemic heart disease without infarction and had initial electrocardiograms showing nonspecific ST and T-wave changes; they had not developed recurrent chest pain or further electrocardiographic abnormalities in the hospital. Of the 3 other patients, 1 had a discharge diagnosis of arthritic musculoskeletal pain and had an initial electrocardiogram with inverted T waves; 1 had a normal initial electrocardiogram and a final diagnosis of postherpetic chest pain; and the third, with a previous history of chest pain and a normal cardiac catheterization 4 years before, had an initial electrocardiogram with an old right bundle branch block and had been discharged with a diagnosis of atypical chest pain. None of the 5 patients had a formal stress test before discharge, which was performed in only 75 (19%) of the 406 patients discharged home directly from the coronary observation unit.

Among the 79 patients transferred to other hospital settings and discharged alive, 3 deaths occurred within 6 months of discharge, 2 of which were cardiac (cardiac survival rate at 6 months 97.6%). The 1 myocardial infarction (1.3%) occurred at 3 months and was fatal. None of the 133 patients accounting for the 143 admissions with a final diagnosis of acute ischemic heart disease without infarction died from cardiac causes during the 6 month follow-up.

DISCUSSION

Patients with acute myocardial infarction inappropriately sent home from the emergency room have a significantly higher mortality rate than admitted patients.[12] Thus, patients with a low probability of myocardial infarction (≤5 to 10%) represent a group in which probabilities are too low for admission to an intensive care unit to be cost-effective,[9] yet often too high for discharge to be safe. They may benefit from admission to a short-stay unit, with monitoring and resuscitation capabilities, but without the other expensive services provided in coronary care units or in full-fledged stepdown or intermediate care units. Precoronary care areas, such as designated beds in the emergency room, were suggested by Lown et al[13] but never developed. A short observation period is attractive because it usually takes no >24 hours to rule out a myocardial infarction and because most complications occur within the same time frame.[11,14]

The coronary observation unit is a safe and adequate setting for patients with suspected cardiac ischemic pain and a low probability of acute myocardial infarction, who represent about one-third of those admitted with chest pain.[15] The low complication rates of our 512 admissions were not surprising, since our electrocardiographic criteria screened out high-risk patients[16] as well as patients eligible for thrombolysis. The 3% rate of acute myocardial infarction was close to

our predetermined goal of 5%, and 83% of the patients were discharged home directly from the coronary observation unit after a mean length of stay of 1.2 days.

During our study period, the coronary observation unit had a 32% occupancy rate of patients with rule-out myocardial infarction. One advantage is that this unit's low-intensity beds were used by other patients when there was not a demand from patients with potential cardiac ischemic pain. By comparison, our 10-bed coronary care unit had a 79% average occupancy rate during this time period. The per diem charges and nurse: patient ratios at our hospital in 1988 were, respectively, $1,040 and 1:1 to 1:2 for the coronary care unit, $625 and 1:3 to 1:4 for the stepdown unit, $450 and 1:5 for the wards, and $415 and 1:5 for the coronary observation unit. Although the true costs of these different units may not be reflected by charges, our new unit has monitoring capabilities that are not available on the regular wards and has lower nursing intensity than the stepdown or the coronary care units, which should reduce true costs.[17] Some patients may have been sent home if the coronary observation unit did not exist, and the cost-effectiveness trade-offs between a possible increase in admission rates versus a shorter length of stay require additional study.

Of the patients discharged home directly from the coronary observation unit, 1.2% had a myocardial infarction within 72 hours, as did 1.4% of the patients discharged home directly from the emergency room in the Multicenter Chest Pain Study.[12] A 24-hour period is adequate to establish a diagnosis in about 99% of patients with acute myocardial infarction,[11] whereas a 12-hour protocol is adequate in 99.5%[15] of patients with a low probability of myocardial infarction, such as nearly all of the coronary observation unit patients.

The fact that 24% of the patients discharged home from the coronary observation unit had a diagnosis of acute ischemic heart disease without infarction must be interpreted in light of the broad criteria used to define this diagnosis, the admission electrocardiograms of these patients and their uneventful clinical courses in the coronary observation unit. Although all patients were discharged after adequate ambulation, only 75 (19%) underwent formal exercise stress tests and none underwent cardiac catheterization. The 6- to 24-month prognosis of patients hospitalized with acute ischemic pain but no infarction is similar to that of patients with infarction.[18] Although stress testing is not perfect in diagnosing coronary artery disease,[19] it is reasonably reliable for estimating prognosis.[20–22] Mandatory but expeditious stress testing is likely to augment the efficiency of coronary observation units.

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Beneficial Effect of Long-Term Beta Blockade After Acute Myocardial Infarction in Patients Without Anterograde Flow in the Infarct Artery

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Previous studies have shown that long-term survival after acute myocardial infarction (AMI) is improved by β-adrenergic blockade and anterograde flow in the infarct artery. This study was done to assess the influence of β blockade on mortality in survivors of AMI without anterograde flow. Over 9.5 years, 113 subjects (87 men and 26 women, aged 26 to 66 years) with AMI and no anterograde flow in the infarct artery and no disease of the other arteries were medically treated for 48 ± 28 (mean ± standard deviation) months. Forty-six patients received long-term β blockade (group I), whereas 67 did not (group II). The groups were similar in age, sex, cardioactive medications, left ventricular performance and infarct artery. Of the 46 group I subjects, 1 (2%) died of cardiac causes; in contrast, 20 (30%) of the group II patients died of cardiac causes (p = 0.007 compared with group I). Thus, in survivors of AMI without anterograde flow in the infarct artery, mortality is markedly reduced by long-term β blockade.

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Since Snow's[1] report over 25 years ago, several studies demonstrated the beneficial effect of long-term β-adrenergic blockade in reducing mortality in survivors of acute myocardial infarction (AMI).[2–5] Although the mechanism by which β blockers accomplish this is unknown, it may be due, at least in part, to their antiarrhythmic effect. Recent studies showed that long-term survival after AMI is improved by the presence of anterograde flow in the infarct artery[6,7]: Survival was excellent in subjects with anterograde flow, whereas it was substantially reduced in those without it. Almost all subjects who died did so suddenly, suggesting an arrhythmic event.[6,7] In support of this, subsequent studies[8,9] showed that survivors of AMI whose infarct arteries were occluded were more likely to have late potentials on signal-averaged electrocardiography (an indicator of enhanced vulnerability to ventricular tachyarrhythmias) than those whose infarct arteries had anterograde flow. Thus, in patients with anterograde flow in the infarct artery, survival after AMI is good, so that long-term β blockade may not exert a beneficial influence. In contrast, survival is decreased in subjects whose infarct artery is occluded; in these persons, long-term β blockade may substantially improve survival. This study was done to test this hypothesis.

METHODS

Patient population: We reviewed the results of all cardiac catheterizations at Parkland Memorial Hospital, Dallas, Texas, from July 1978 to December 1987. Of the 3,195 patients, 135 were studied 1 to 150 days after AMI and were found to have no anterograde flow in the infarct artery and no disease of the other coronary arteries. On hospital admission, 15 received intravenous thrombolytic therapy (tissue plasminogen activator in 5, streptokinase in 10). None had coronary angioplasty. Twenty patients had coronary artery bypass surgery for medically refractory angina and were excluded from analysis, because the patency of their grafts was uncertain. Long-term follow-up information was not available in 2 of the 115 patients treated medically.

The remaining 113 patients (87 men and 26 women, aged 26 to 66 years) — each of whom had AMI

TABLE I Comparison of the Two Patient Groups

	Group I Beta Blockade (n = 46)	Group II No Beta Blockade (n = 67)	p Value
Age (years)	45 ± 10	47 ± 11	NS
No. of men	36 (78%)	51 (76%)	NS
Time from infarction to catheterization (days)	30 ± 27	30 ± 29	NS
Duration of follow-up (mos)	54 ± 27	43 ± 29	NS
Medications			
Calcium antagonists	15 (33%)	31 (46%)	NS
Long-acting nitrates	24 (52%)	39 (58%)	NS
Aspirin	17 (37%)	23 (34%)	NS
Antiarrhythmic agents	4 (9%)	19 (28%)	0.06
Left ventricular volumes			
End-diastolic volume (ml/m^2)	72 ± 16	72 ± 25	NS
End-systolic volume (ml/m^2)	33 ± 13	38 ± 21	NS
Ejection fraction	0.55 ± 0.10	0.50 ± 0.12	NS
Infarct artery			
Left anterior descending	14 (30%)	26 (39%)	NS
Left circumflex	8 (18%)	10 (15%)	NS
Right	24 (52%)	31 (46%)	NS
Mortality			
Total	3 (7%)	22 (33%)	0.007
Cardiac causes	1 (2%)	20 (30%)	<0.01

All data are mean ± 1 standard deviation, unless otherwise stated.
NS = not significant.

and no anterograde flow in the infarct artery and no disease of the other coronary arteries — form the basis of this report. Forty-six patients (group I) received β blockers (propranolol in 18, metoprolol in 14, atenolol in 9, timolol in 3, and nadolol in 2) beginning before hospital discharge and continuing for the duration of the study, whereas the other 67 (group II) did not receive them. The decision to give β blockers was made by each patient's primary physician. Of the 46 group I patients, 4 (9%) were maintained on antiarrhythmic agents: quinidine in 2 and procainamide in 2. Of the 67 group II patients, 19 (28%) were given antiarrhythmic therapy: procainamide in 11, quinidine in 4, tocainide in 3 and both quinidine and tocainide in 1.

Of the 46 group I subjects, 13 (28%) underwent cardiac catheterization because they were ≤40 years old, 20 (44%) because of postinfarction angina, 7 (15%) as a routine after thrombolytic therapy, and 6 (13%) because of a positive submaximal exercise test result. Of the 67 group II patients, 15 (22%) underwent cardiac catheterization because they were ≤40 years old, 29 (43%) because of postinfarction angina, 8 (12%) as a standard procedure after thrombolytic therapy, and 15 (23%) because of a positive submaximal exercise test result. Each patient's record was reviewed, and each living subject was interviewed. For the 25 subjects who died, the next of kin was interviewed.

Variables assessed: At catheterization, left ventricular volumes and ejection fraction were quantitated[10,11] and coronary arteriography was performed. During follow-up, a record of each subject's cardioactive medications was kept, and the occurrence of death was noted. Sudden cardiac death was defined as the occurrence of death within 1 hour of the onset of symptoms, generally before the availability of medical attention. It occurred (1) in the presence of witnesses with or without confirmation of arrhythmia or (2) unwitnessed, when the patient was alive and well when last seen and soon after was found dead.[12]

Statistical methods: All data are reported as mean ± 1 standard deviation. Estimated survival curves were generated with the Cox model proportional-hazards analysis. A stepwise proportional-hazards analysis determined the independent correlates of survival. The characteristics of the 2 groups were compared with the chi-square test for categorical variables and Student's *t* test for continuous variables. For all analyses, a p value <0.05 was considered significant.

RESULTS

The patients receiving β blockers (group I, n = 46) were similar to those not receiving them (group II, n = 67) in age, sex, cardioactive medications, left ventricular volumes and ejection fraction, duration of follow-up and infarct artery (Table I). Group I patients had a better survival than group II patients (Table I, Figure 1). By stepwise discriminant analysis, the absence of treatment with β blockers was the most significant predictor of mortality. Other significant discriminants of increased mortality were (1) concomitant antiarrhythmic therapy, and (2) the left anterior descending or left circumflex coronary artery as the infarct vessel. The characteristics of the 25 patients who died are listed in Table II.

TABLE II Characteristics of the 25 Patients Who Died

Pt. No.	Age (yr) at AMI & Sex	LVEDV (ml/m²)	LVESV (ml/m²)	LVEF	Infarct Artery	Collateral Filling of Infarct Artery	Time from MI to Death (mos)	Mode of Death	Group
1	53M	63	25	0.60	LC	+	51	Sudden	I
2	54M	84	37	0.56	Right	+	3	Cancer	I
3	54F	72	39	0.46	Right	+	27	Cancer	I
4	40M	66	46	0.31	LAD	+	14	Sudden	II
5	40M	87	52	0.40	LAD	+	19	Sudden	II
6	50M	79	58	0.27	LAD	+	40	Sudden	II
7	64M	41	12	0.71	LAD	+	57	Sudden	II
8	26M	137	67	0.51	LAD	+	13	Sudden	II
9	65M	143	118	0.18	LAD	–	72	Sudden	II
10	40F	63	11	0.82	LAD	+	32	Sudden	II
11	55M	32	14	0.58	LAD	–	64	Sudden	II
12	55M	131	80	0.38	LAD	+	71	Sudden	II
13	35M	101	50	0.51	LAD	+	6	Sudden	II
14	46M	68	43	0.37	LAD	+	25	Sudden	II
15	37M	91	53	0.41	LAD	–	22	Sudden	II
16	57F	122	74	0.39	LC	+	10	Sudden	II
17	57M	62	27	0.57	LC	+	93	Sudden	II
18	58M	65	30	0.54	LC	+	2	Sudden	II
19	47M	97	61	0.37	LC	+	62	Sudden	II
20	42M	59	28	0.52	Right	+	4	Sudden	II
21	64F	NA	NA	NA	Right	+	1	Sudden	II
22	35M	107	71	0.33	Right	+	61	Sudden	II
23	65M	51	20	0.61	Right	–	1	Sudden	II
24	39M	76	33	0.56	LC	+	26	Trauma	II
25	44F	82	45	0.67	Right	+	6	Cancer	II
Mean ± SD	49 ± 11	82 ± 29	45 ± 25	0.48 ± 0.15			31 ± 27		

AMI = acute myocardial infarction; LAD = left anterior descending; LC = left circumflex; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; NA = not available; SD = standard deviation.

The left anterior descending coronary artery was the infarct vessel in 40 patients (14 in group I, 26 in group II), the left circumflex in 18 (8 in group I, 10 in group II), and the right coronary artery in 55 (24 in group I, 31 in group II) (Table III). The paucity of left circumflex disease has been described.[13,14]

Angiographic evidence of collateral filling of the distal infarct artery was noted in 41 of 46 patients (89%) in group I and 51 of 67 patients (76%) in group II (p = not significant), but it did not influence survival: 17 of the 21 patients who died of cardiac causes had angiographic evidence of collateral filling of the distal infarct artery (Table II).

As noted previously, 2 of our 115 patients were lost to follow-up. Both had an occluded right coronary artery; 1 received long-term therapy with timolol, whereas the other was not given β blockade.

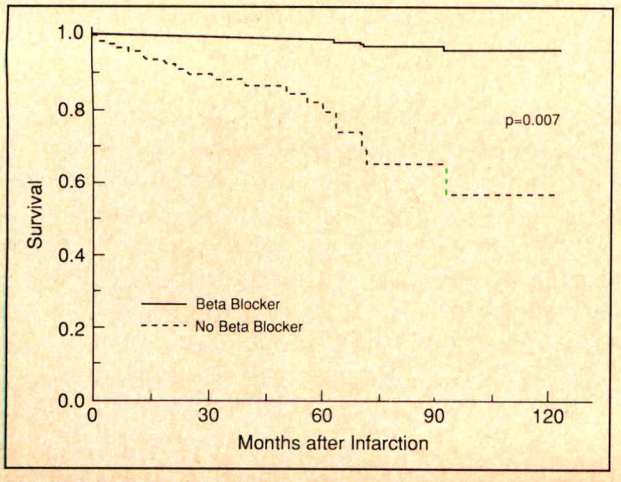


FIGURE 1. A life-table survivorship analysis for the 2 groups. Group I had a significantly better survival than group II.

DISCUSSION

Our data, obtained from 113 patients, demonstrate a markedly beneficial effect of long-term β-adrenergic blockade on survival in subjects with AMI and an occluded infarct artery. Of the 46 patients given β blockers after AMI (group I), only 1 (2%) died of a cardiac cause over the ensuing 3 to 113 months (average 54 ± 27). In contrast, of the 67 patients not given β blockade (group II), 20 (30%) died of a cardiac cause during a follow-up period of similar duration (46 ± 33 months) (Table 1, Figure 1) (p = 0.007 compared with group I). Thus, although the groups were similar in age, sex, infarct vessel, left ventricular volumes and ejection fraction, and duration of follow-up, they differed markedly in survival.

TABLE III Comparison of the Two Groups for Each Infarct Artery

	Left Anterior Descending		Left Circumflex		Right Coronary	
	Group I (n = 14)	Group II (n = 26)	Group I (n = 8)	Group II (n = 10)	Group I (n = 24)	Group II (n = 31)
Age (years)	45 ± 11	47 ± 11	45 ± 8	46 ± 11	45 ± 9	49 ± 10
No. of men	10 (71%)	20 (77%)	7 (88%)	7 (70%)	19 (79%)	24 (77%)
Duration of follow-up (mos)	56 ± 30	37 ± 24	54 ± 29	46 ± 33	52 ± 25	48 ± 31
Left ventricular ejection fraction	0.52 ± 0.12	0.49 ± 0.16	0.54 ± 0.04	0.49 ± 0.10	0.57 ± 0.09	0.52 ± 0.08
Mortality	0 (0%)	12 (46%)*	1 (12%)	5 (50%)*	2 (8%)	5(16%)

*$p < 0.01$ in comparison to group I
All values are mean ± 1 standard deviation, unless otherwise stated.

By stepwise discriminant analysis, survival correlated most significantly with β blockade. Two other variables were statistically significant, but less powerful, predictors of an increased mortality: the left anterior descending or left circumflex as the infarct artery (Table III) and concomitant antiarrhythmic therapy. This is in agreement with previous studies,[6] which showed that mortality was high in subjects with occluded left anterior descending or left circumflex coronary arteries. Antiarrhythmic agents may have been reserved for subjects believed to be at greatest risk of having an arrhythmic event, such as those with depressed left ventricular systolic performance. However, the groups were similar with respect to the incidence of depressed left ventricular function: 4 of 46 group I subjects (9%) and 11 of 67 group II patients (16%) had ejection fractions <0.40 (p = not significant). Alternatively, these agents may have been proarrhythmic, aggravating the propensity for ventricular tachyarrhythmias.[15] However, of the 25 patients who died, only 10 received antiarrhythmic agents, whereas 22 did not receive β blockers, so that survival was most closely linked to β blockade.

Previous studies have shown that long-term survival after AMI is markedly improved by (1) β blockade,[2–5] and (2) anterograde flow in the infarct artery,[6,7] both of which may exert their beneficial influence by reducing the incidence of ventricular tachyarrhythmias. The evidence that β blockade acts in this manner is provided by the Norwegian trial, in which timolol induced a 70% decrease in the incidence of sudden death.[16] Long-term administration of some β blockers prolongs the action potential duration and effective refractory period of the ventricle,[17] but whether these effects, alone or in combination, contribute to the antiarrhythmic action of β blockers in patients after AMI is unclear.

Successful coronary reperfusion in patients with AMI reduces the incidence of inducible ventricular tachyarrhythmias and sudden death.[18,19] Furthermore, patients without anterograde flow in the infarct artery have a higher incidence of late potentials than those with anterograde flow.[8] In the present study, survival after AMI was dramatically improved by the use of β blockade in patients without anterograde flow in the infarct artery (Table I, Figure 1). Although our data do not allow us to assess the mechanism of death in our patients, it is likely that an arrhythmia was the terminal event in most, since 21 of 25 died suddenly (Table II).

Our study has certain limitations. First, it is a retrospective assessment of patients with AMI and angiographic evidence of an occluded infarct artery. We cannot exclude the possibility of unrecognized bias in the selection of patients. Our results must be confirmed in a properly performed prospective evaluation. Second, we limited our analysis to subjects with disease of only the infarct artery; whether patients with multivessel coronary artery disease will demonstrate similar results is unknown. Third, although we examined all subjects over a 9.5-year period who sustained AMI and underwent cardiac catheterization, not all patients with AMI at our hospital during that time underwent this procedure. We cannot exclude the possibility that our results may have been different if all patients had undergone catheterization after AMI. At the same time, our study has certain strengths. It provides follow-up data over an extended period (48 ± 28 months), with 38 of the patients followed for >5 years.

Our findings may have substantial implications for the manner in which patients are managed after AMI. Long-term survival after AMI appears to be excellent in subjects (1) with anterograde flow in the infarct artery, and (2) without anterograde flow provided that a β blocker is given. If neither anterograde flow nor β blockade is present, survival is dramatically reduced (Table I, Figure 1), especially in the patient whose infarct artery is the left anterior descending or left circumflex (Table III). Therefore, it may be prudent in the days to weeks after AMI to perform angiography to determine if the infarct artery has anterograde flow. If anterograde flow is present, survival is good, and long-term β blockade may be superfluous, costly and unnecessary. On the other hand, if anterograde flow is absent and cannot be restored (pharmacologically or mechanically), long-term β blockade may profoundly

improve survival. These possibilities await confirmation in properly designed prospective clinical trials.

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Diurnal Variations of Neurocardiac Rhythms In Acute Myocardial Infarction

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To determine the diurnal pattern of cardiac autonomic tone in acute myocardial infarction (AMI), this study examined the power spectrum of heart rate (HR) variability in 24 patients during a single 24-hour segment within 4 days of AMI. Patients were nonrandomly allocated to a group (n = 14) without autonomic drugs and to a group (n = 10) already receiving β blockers at the time of AMI. With use of autoregressive modeling, the power spectrum of HR variability was computed from continuous 1-hour electrocardiographic segments recorded at equally spaced intervals; 7 to 8 A.M., 3 to 4 P.M., and 11 to 12 P.M. All patients were supine, awake and pain free during recordings. There were no differences in HR, HR variance or the low-frequency peak power (0.06 to 0.1 Hz) from one temporal sequence to another. For the patients not taking β blockers, the high-frequency peak power (0.2 to 0.36 Hz) or vagal component increased significantly from 3 P.M. to 11 P.M. (28 ± 11 to 45 ± 20 beats/min$^2 \cdot$ Hz^{-1}, $p < 0.01$). There was a significant decrease in the low- to high-frequency peak power and area ratios from 3 P.M. to 11 P.M. All power spectral parameters in the patients taking β blockers remained unchanged over 24 hours. There was significantly heightened vagal modulation of sinus node activity in those receiving β blockers, especially at 7 A.M. and 3 P.M.

The data suggest that under steady-state wakeful conditions in the early recovery phase after an AMI, vagal tone is more pronounced during the late evening hours with a possible shift to relative sympathetic dominance during early morning and midafternoon hours. Beta blockade appears to dampen any cyclic variation of neurocardiac rhythms as measured by the HR autospectrum.

(Am J Cardiol 1991;68:155–160)

Recent data show a characteristic circadian pattern to the time of onset of acute vascular events such as acute myocardial infarction (AMI),[1,2] unstable angina,[3] sudden death,[4] transient unprovoked myocardial ischemia[5] and stroke.[6] These events occur more often during morning hours from wakefulness (6 to 7 A.M.) to noon. Most studies have focused on either the time of event onset or the diurnal behavior of putative triggers.[7,8] The mechanisms by which susceptible patients are supposedly protected during the nonvulnerable early afternoon and late evening wakeful hours has received little attention. Moreover, few studies have addressed circadian patterns in the postevent phase.[9,10] Heart rate (HR) variability has a distinct circadian rhythm.[11] It is also recognized as an independent predictor of outcome events after AMI.[12] However, as a time domain parameter, HR variability is a somewhat crude measure of cardiac autonomic tone. To determine a more precise balance between sympathetic and vagal input to sinus node activity, the heart's instantaneous beat-to-beat fluctuations can be transformed into its frequency components using power spectrum analysis.[13,14]

Power spectrum analysis of a discrete time series requires steady-state conditions. We therefore examined the power spectrum of HR variability over 1 continuous hour of steady-state wakeful but rest supine conditions every 8 hours at 7 to 8 A.M., 3 to 4 P.M. and 11 to 12 P.M. in 24 patients within 96 hours of an AMI.

METHODS

Patients: The study group consisted of 24 patients with AMI admitted to our coronary care unit. Diagnosis was based on ≥2 of the following criteria: prolonged (>30 minutes) ischemic pain; electrocardiographic changes with typical evolution of pathologic Q waves or persistent symmetrical T-wave inversion or both; ≥2 successive samples of creatine kinase-MB levels >10% of a total creatine kinase >250 IU. Of the 24

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TABLE I Clinical And Demographic Data

	Without β Blockers (n = 14)	With β Blockers (n = 10)	p Value
Age (years)	65 ± 8.1	61 ± 6.8	NS
Men/women	12/1	9/1	NS
Site of myocardial infarction			
Anterior	4	2	
Inferior	10	6	NS
Non-Q-wave	0	2	
Peak creatine kinase (IU)	1698 ± 1097	988 ± 777	NS
Received thrombolytic therapy	58%	35%	NS
Killip class			
I or II	13	10	NS
III or IV	1	0	
Heart rate (beats/min)	78.2 ± 11.3	59.5 ± 7.5	<0.01

NS = not significant.

patients, 10 were already receiving a β blocker before the acute event and they were maintained on the drug at the time of the study. None of the patients were taking other autonomic drugs. The entry criteria included: patients in sinus rhythm with only rare ventricular premature contractions (<6 per hour); patients free of any clinical instability such as shock, severe heart failure or persistent chest pain; and patients able to rest comfortably in bed for 1-hour periods without undue distraction or exaggerated changes in movement or posture. Although not randomly allocated, patients were nevertheless grouped according to whether they were or were not taking β blockers. The clinical characteristics of both groups are listed in Table I. There were no significant group differences in age, sex distribution, site of infarction, Killip class[15] or peak creatine kinase levels. As expected, there was a significantly reduced HR in the group taking β blockers (59 beats/min ± 7 vs 78 beats/min ± 11, p <0.01).

Study protocol: All patients were awake and resting supine without angina or discomfort during each hourly recording session. A continuous electrocardiographic record over 1 complete hour was collected every 8 hours at 3 to 4 P.M., 11 to 12 P.M. and 7 to 8 A.M. The analog record was fed into a Teac R61 FM tape recorder and stored for off-line analysis. All patients were in a postprandial state. A light meal was given at 8 A.M., 12 noon and 5 P.M.

Signal processing and power spectrum computation: The electrocardiographic signals were passed through analog filters with their 3-decibel cutoff frequency set to 1 to 100 Hz. The filtered electrocardiographic signal was digitized using a 12 bit analog-to-digital converter at a rate of 1 kHz (1,000 samples per second). All signal processing and power spectral computations were performed on an IBM/AT computer equipped with a 40 MB hard disk. A peak detection algorithm for locating the R wave was implemented in the software. A beat-to-beat HR series was computed from the interval tachogram. The time domain HR variability signal was visually verified to be free of artifacts before further processing. If occasional ventricular ectopic beats were present (<6 beats/hour), a nonlinear smoothing was applied whereby the missing value was equated as the average of the previous beat and the succeeding beat.[16]

We computed the power spectrum of HR variability using the autoregressive modeling method.[14,17] Because the computational technique requires an evenly spaced time series, the beat-to-beat HR was resampled using linear interpolation to obtain an equally sampled time domain signal spaced 0.5 second apart. The power spectrum was computed from HR variability data of 256 samples (128 seconds). The power contained in the frequency band from direct current to 0.02 Hz (referred to as direct-current power) often gives spuriously low values due to 1/f noise in the low- and high-frequency bands.[18] To minimize such effects we passed equally sampled HR variability signals through a second order high-pass Butterworth filter with a cut-off at 0.02 Hz, twice, initially in the forward direction and with the time series reversed during the second pass. The overall transfer function of such a procedure has a zero phase shift and provides a sharp filtering operation.[19] An autoregressive model was fitted to the demeaned and filtered HR variability signal.

The following indexes were computed to characterize the information contained in the power spectrum: the maximal value of the peak power in the low- and high-frequency bands; the minimal value between the 2 peaks, denoted as the point separating the low- and high-frequency bands; the area under each band, computed by numerically integrating the power under each peak; and a percent measure of the area under each peak, obtained by dividing the power under each band by the total energy contained in the whole spectrum. Because the peaks of the autospectra are clearly defined, the frequency location for each of the 2 peaks in the spectrum was also determined. Mean values (± standard deviation [SD]) of all variables were computed by averaging 20 to 30 samples (2.2 minutes each) of spectral variables obtained for each recording epoch.

Statistical analysis: HR variability for each patient was measured using both time domain descriptor (i.e., the mean ± SD) and frequency domain indexes. The means ± SD of these descriptors were computed over 1 hour for each recording epoch. Changes in mean HR, amplitudes of low- and high-frequency peaks, peak power and area ratios, and location (frequency) of the 2 spectral peaks were compared using a 2-tailed Student's *t* test. A p value <0.05 was accepted as significant.

TABLE II Diurnal Changes in Autospectral Indexes in Patients with Acute Myocardial Infarction

	HR (beats/min)	HR (SD)	LF Peak	HF Peak	LF:HF Peak Ratio	LF:HF Area Ratio	Frequency (Hz) LF	Frequency (Hz) HF
Without β Blockers (n = 14)								
7–8 A.M.	76 ± 8.9	1.7 ± 1.4	82 ± 21	35 ± 20	2.6 ± 1.6	2.5 ± 1.6	0.07 ± 0.009	0.3 ± 0.06
3–4 P.M.	76 ± 9.2	3.0 ± 1.3	79 ± 14	28 ± 11	3.4 ± 1.3	2.7 ± 1.1	0.07 ± 0.008	0.3 ± 0.07
11–12 P.M.	78 ± 11.3	2.5 ± 0.8	75 ± 23	45 ± 20*	2.1 ± 1.3*	1.7 ± 0.8*	0.06 ± 0.006	0.3 ± 0.07
With β Blockers (n = 10)								
7–8 A.M.	60 ± 8.4†	2.6 ± .96	64 ± 13†	54 ± 17†	1.7 ± 0.90†	1.6 ± 0.8	0.08 ± 0.01†	0.32 ± 0.05
3–4 P.M.	62 ± 7.9†	2.7 ± .95	59 ± 15†	45 ± 15†	1.8 ± 1.2†	1.3 ± 0.7†	0.08 ± 0.01	0.31 ± 0.04
11–12 P.M.	59 ± 7.5†	2.6 ± 1.1	64 ± 13	54 ± 27	1.9 ± 1.6	1.6 ± 1.1	0.07 ± 0.01	0.31 ± 0.04

*$p < 0.05$ when compared with values at 3 P.M.; †$p < 0.01$ when compared with corresponding values in the group not receiving β blockers.
HF = high frequency; HR = heart rate; LF = low frequency; Peak = refers to peak power expressed as (beats/min)²/Hz; SD = standard deviation.

RESULTS

Table II lists the temporal sequence for both time domain and power spectral indexes of HR variability. There were no temporal changes in HR, HR SD or low-frequency peak power in patients with or without β blockers. There were also no significant diurnal shifts in the frequencies at which the peak spectral components oscillated. Respiratory frequency (an oscillatory stimulus known to influence cardiac vagal efferent input) was constant (0.30 to 0.31 Hz) regardless of the time of day. However, the high-frequency (vagal) peak power in patients not taking β blockers increased significantly from 3:00 P.M. to 11 P.M. (28.9 to 44.6 beats/min^2 · Hz^{-1}, $p < 0.05$). During the same steady-state conditions at 7:00 A.M. the following morning, the high-frequency peak power had decreased insignificantly to 35 beats/min^2 · Hz^{-1} ± 20. The low- to high-frequency power ratio is an expression of the relative balance between sympathetic and vagal modulation of HR control. Here, there was a significant decrease in both the peak power ratio (3.4 to 2.1) and area ratio (2.7 to 1.7) from 3:00 P.M. to the late evening hour (Table II, Figure 1). There was an insignificant increase in the low-frequency peak power from late evening (11:00 P.M.) to early morning (7:00 A.M.). There were no significant differences in the peak amplitude, areas or ratios of any autospectral component between 7 to 8 A.M. and 3 to 4 P.M.

Regardless of the time of day, HR was always significantly lower in the patients taking β blockers (Table II). However, HR variability or SD during all temporal sequences was similar to patients not taking β blockers. Two observations can be made about the patients who were already receiving β blockers. First, the high-frequency (vagal) peak power was significantly higher in the group with than without β blockers at 7:00 A.M. and 3:00 P.M. This, coupled with a relatively depressed low-frequency component in patients taking β blockers, re-

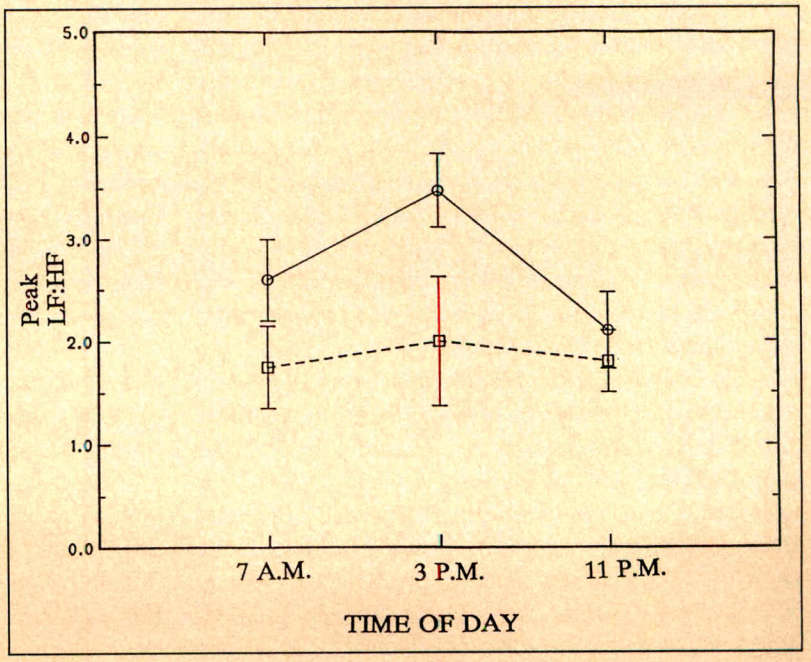


FIGURE 1. Diurnal changes in the autospectral peak power of low-frequency component (LF) to high-frequency component (HF) ratio. *Open circles*, group not taking β blockers (n = 14); *open squares*, group taking β blockers (n = 10). Group mean ± standard deviation differs significantly at 7 A.M. and 3 P.M. ($p < 0.05$).

sulted in a decreased peak and area ratio especially at 3:00 P.M. (Table II, Figure 1). Second, β blockade appeared to dampen or suppress any diurnal oscillations in sympathovagal modulation of HR control under these steady-state conditions (i.e., no change in either the high-frequency peak power or low- to high-frequency ratio was seen among the equally spaced time intervals).

Figure 2 (A to C) illustrates an example of temporal changes in the power spectrum of HR variability in a patient not taking a β blocker. Note the consistency of the autospectral pattern throughout each 1-hour sequence. This attests, in part, to the steady-state conditions obtained during the recording intervals. Each autospectral plot in the stacked series represents continuous data over a 2.2-minute interval. Figure 2C illustrates the increase in the energies contained in the high-frequency band at 11:00 P.M., reflecting dominance of vagal modulation during the late evening hours. This is compared with the relative sympathetic dominance at 3:00 P.M. and less so at 7:00 A.M. (Figure 2, A and B, respectively).

DISCUSSION

These data show that under steady-state wakeful conditions, there is diurnal oscillation of cardiac autonomic tone in patients with AMI. Vagal tone appears more pronounced during late evening (11 to midnight), whereas an apparent imbalance toward sympathetic dominance is seen during midafternoon (3 to 4 P.M.) hours and less so from 7 to 8 A.M. In patients already receiving β blockers, vagal modulation of sinus node activity as measured by the HR autospectrum is augmented and there appears to be less variability of neurocardiac rhythms throughout the day.

The recent interest in circadian or diurnal rhythms has focused mainly on the timing of acute cardiovascular events.[1-6] Episodes of transient myocardial ischemia, sudden death or AMI occur more often between 6 A.M. and 12 noon. Although similar circadian patterns have been observed for such putative triggers as the rate-pressure product,[7] catecholamines[8] and platelet aggregability,[20] the temporal sequence of these variables, once the acute event has occurred, is less well known. In this context the 24-hour HR variability after acute infarction has been shown to follow a diurnal periodicity.[10] Furthermore, HR variability is recognized as a powerful predictor of outcome events after infarction.[12,21] In a recent study of ambulant hypertensive subjects, the 24-hour HR variability record was transformed into power spectral estimates.[22] The data showed a rapid early morning increase in sympathetic compared with vagal tone. Conversely, there was an increased vagal tone at night. Using the same methodology, Hayano et al[23] reported enhanced vagal tone during morning waking hours, although little or no diurnal variation was seen in the low-frequency (sympathetic) component. The latter study was conducted under conditions of controlled, regulated respiration in young healthy men. Despite the apparent disparity between these studies, it appears, nonetheless, that autonomic influences play a role in the wake-activity diurnal cycles whether part of endogenous biologic rhythms or externally driven. Recent evidence suggests that the onset of AMI is most likely to occur within 2 hours of waking regardless of the patient's physical state.[24] In virtually all circadian patterns reported, there is, invariably, a brief late afternoon surge in the incidence of event onset.[1-3] As far as one can judge, this is unrelated to any sleep-wake-activity cycle. The data reported here mirrors these observations by demonstrating heightened sympathetic tone (or vagal suppression) not only at 7 to 8 A.M., but also at 3 to 4 P.M. under similar wakeful, steady-state conditions.

Effects of beta blockade: It has been shown that factors including advanced age, diabetes mellitus, smoking and certain drugs such as β blockers modify the circadian profile of coronary event onset.[25] Patients already receiving β blockers have the first symptoms of AMI in a randomized distribution throughout the day.[26] It has even been suggested that β blockade may confer a different periodicity to the timing of ischemic events.[27] For instance, whereas the time of onset for AMI has a 24-hour periodicity, β blockade may shift this periodicity to a 5- or 6-hour cycle. In a recent randomized clinical trial, propranolol reduced the overall incidence of sudden cardiac death by about 22%.[28] Propranolol reduced the sudden death rate by 44% between the hours of 2 A.M. and 2 P.M., although paradoxically, there was an 18% increase in the sudden death rate between 2 P.M. and 2 A.M. in the propranolol compared with the placebo group. Our data reveal 2 characteristics in the patients who took β blockers. First, there was no significant diurnal variation in sympathovagal balance in these patients. Second, regardless of the time of day, the vagal or high-frequency component was always higher in amplitude in patients already taking β blockers than in those who did not. Augmentation of the high-frequency (vagal) component with β blockers has recently been observed by others.[29]

Study limitations: Three hours of data, no matter how evenly spaced, are but brief glimpses of a 24-hour cycle. On the other hand, circadian rhythms based on continuous ambulatory monitoring contain sequences of a time event series in which steady-state conditions are difficult to control. For instance, physical activity, emotional stress, nutritional state or posture may have considerable impact on spontaneous diurnal patterns of HR variability. This is particularly relevant if one wishes to determine the power spectrum of beat-to-beat os-

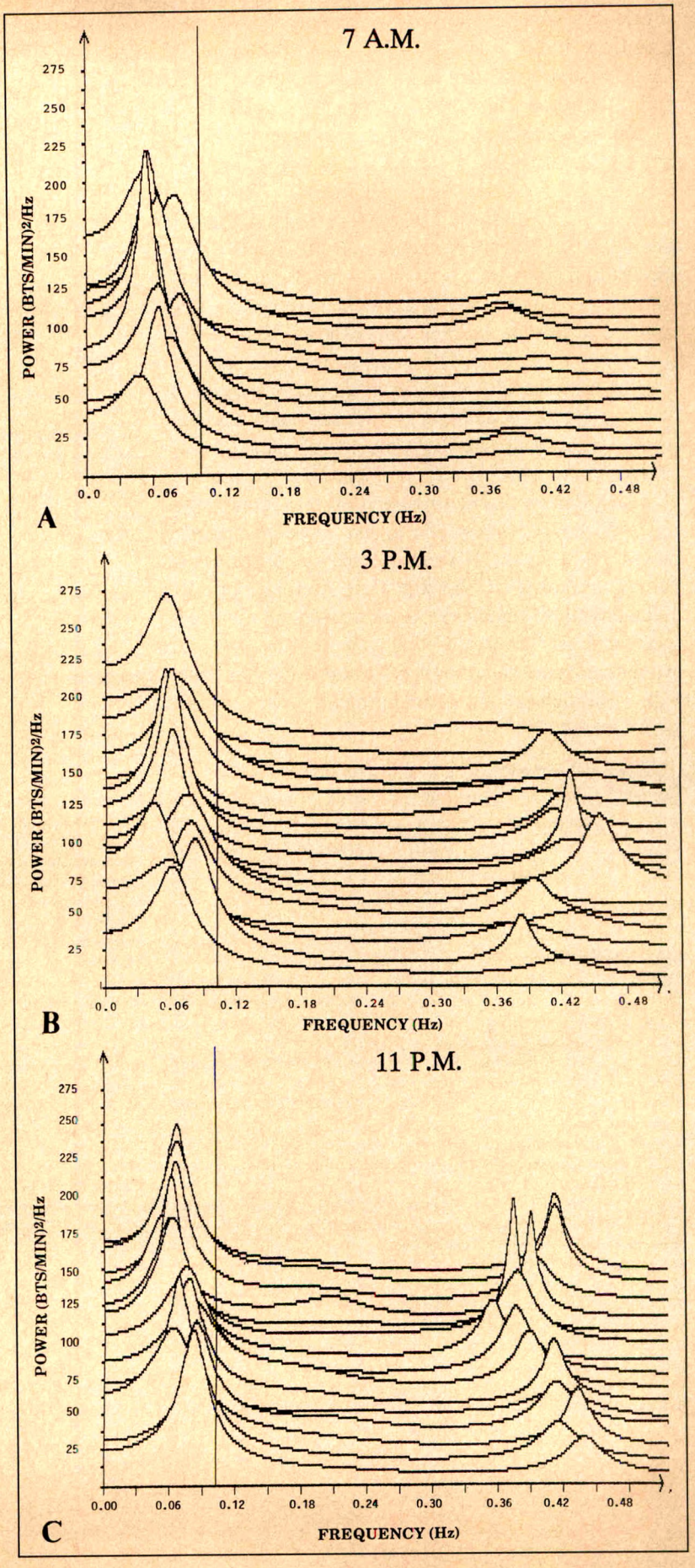


FIGURE 2. Stacked series of heart rate autospectra in a patient not taking β blockers. Note that in all cases, the low-frequency peaks are to the left of the 0.1-Hz *vertical line.* Each spectral plot represents 2.2 minutes of continuous RR intervals. *A,* dominant low-frequency peaks at 7 A.M.; *B,* continued dominance of low-frequency power at 3 P.M.; *C,* a shift to a more balanced peak power of low- and high-frequency component ratio at 11 P.M.

cillations in which the analysis necessitates steady-state conditions. In this study, care was taken to optimize the signal to noise ratio and ensure that data was acquired during identical quiescent states equally spaced over a 24-hour period. Care was also taken to minimize signal artifacts, external stimuli and arrhythmias.

Relevance: As an early predictor of postinfarction outcome events, HR variability contains hidden rhythms that reflect autonomic cardiac tone. Power spectrum analysis is a useful signature of sympathovagal balance and thus provides a clearer picture of autonomic control than HR variability alone.[13] This study shows that while mean HR and its variance or SD remained constant during separate quiescent periods of the day, significant changes in sympathovagal modulation of sinus node activity were taking place. These changes may play a role in facilitating subsequent events. Although this descriptive study was limited to a single 24-hour segment during an evolving ischemic process, whether the HR autospectrum and its diurnal pattern improves on the predictive accuracy of HR variability alone remains to be seen. Using power spectrum analysis, Lombardi et al[30] showed an increased sympathetic tone persisting for 2 weeks after infarction, with restitution toward normal sympathovagal balance by 6 months.

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Coronary Recanalization Rate After Intravenous Bolus of Alteplase in Acute Myocardial Infarction

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The demonstration in animals that recombinant tissue-type plasminogen activator produces prolonged thrombolysis after its clearance from the circulation has prompted a few pilot studies of bolus administration in patients. Alteplase (bolus dose of 70 mg) resulted in the highest recanalization rate in our previous pilot study comparing bolus doses of 50, 60 and 70 mg of alteplase in patients with acute myocardial infarction. The aim of the present trial was to assess the efficacy and safety of the same bolus dose in a larger number of patients. A further objective was to study the angiographic reocclusion rate at 12 to 24 hours in patients who had a recanalized infarct-related coronary artery at 90 minutes and were randomized at that time to a bolus dose or an infusion for 3 hours of 30 mg of alteplase.

Sixty patients with acute myocardial infarction and angiographically documented total occlusion of the infarct-related coronary artery before thrombolysis were treated within 5 hours of onset of symptoms with an intravenous 70-mg bolus dose of alteplase (or 80 mg if body weight was ≥90 kg). Each patient received 5,000 IU of heparin intraarterially and 100 mg of aspirin by mouth before administration of alteplase. Coronary angiography was repeated 60 and 90 minutes after alteplase administration. The recanalization rate of the infarct-related coronary artery was 55% (95% confidence interval, 43 to 66%) at 60 minutes and 48% (95% confidence interval, 37 to 60%) at 90 minutes. Pretreatment levels of lipoprotein (a) were not significantly related to recanalization. Twenty-three patients, who had a patent infarct-related coronary artery during 90-minute angiography and did not require immediate coronary intervention, were then given an additional 30 mg of alteplase, randomly either as an intravenous bolus dose or as an intravenous infusion over 3 hours. Heparin treatment was continued in randomized patients with an intravenous infusion of 1,000 IU of heparin per hour between the time of the 90-minute angiography and the control angiography at 12 to 24 hours. At this final angiography, reocclusion of the infarct-related coronary artery was seen in 1 patient randomized to alteplase infusion (reocclusion rate 4%). Plasma fibrinogen (mean ± standard deviation) before and 90 and 270 minutes after a bolus dose of alteplase was 2.74 ± 0.56, 1.59 ± 0.85 and 1.64 ± 0.84 g/liter, respectively, when assessed as total clottable protein, and 2.85 ± 1.04, 0.77 ± 0.73 and 1.01 ± 1.06 g/liter, respectively, when measured by a clotting rate assay. Only minor bleeding was observed in 65% (95% confidence interval, 53 to 75%) of patients and occurred primarily at puncture sites. In 6 patients a transient decrease of systolic blood pressure ≤90 mm Hg was observed during the first 90 minutes. There were no deaths within 14 days. In considering the recanalization rates obtained in this study, a 70-mg bolus injection of alteplase does not appear to be an optimally effective dosage regimen in the treatment of acute myocardial infarction.

(Am J Cardiol 1991;68:161–165)

Because recombinant tissue-type plasminogen activator (rt-PA) is rapidly cleared from the circulation with an initial half-life of only a few minutes,[1] treatment with this thrombolytic drug is usually by infusion. The currently recommended dosage regimen of single-chain rt-PA (alteplase) for the treatment of acute myocardial infarction is an intravenous infusion of 60, 20 and 20 mg/hour over 3 hours with an initial bolus of 10% of the total dose. With this dosage regimen, the coronary recanalization rate at 90 minutes, which corresponds to the administration of 70 mg of alteplase, was 71% in 83 patients.[2]

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The thrombolytic effect of rt-PA was found to be sustained beyond its time of clearance from the circulation in animal thrombosis models[3–5] and in patients with myocardial infarction.[6] Effective thrombolysis after bolus administration or short infusion of rt-PA has been reported in animals.[4,5,7–10] More recently, the effects of intravenous bolus injection of rt-PA have been investigated in a small number of patients with acute myocardial infarction[11–13] and with pulmonary embolism or deep vein thrombosis.[14] Because the effect of bolus alteplase (single-chain rt-PA) on coronary recanalization had not been investigated in patients, we compared the efficacy in terms of angiographic coronary recanalization of alteplase given in a bolus dose of 50 mg (29 patients), 60 mg (28 patients) and 70 mg (25 patients) in a pilot clinical study.[13] Because the highest recanalization rate (72%) was obtained with a 70-mg bolus dose of alteplase, the aim of the present trial was to expand this preliminary study in a larger number of patients using the 70-mg bolus dose. Because early reocclusion occurred in 22% in another pilot study with bolus alteplase despite concomitant intravenous administration of acetylsalicylic acid and heparin,[11] a further objective of the present trial was to determine whether a second dose of alteplase administered at 90 minutes, either as a bolus or an infusion over 3 hours, would prevent early angiographic reocclusion (12 to 24 hours).

METHODS

Patient selection and administration of drugs: Patients between 21 and 70 years old were eligible for participation if severe chest pain characteristic of myocardial ischemia persisted for ≥30 minutes and provided that thrombolytic treatment could be started within 5 hours after the onset of symptoms. ST-segment elevation of ≥0.2 mV (60 ms after the J point) in ≥2 adjacent electrocardiographic leads had to be present. Neither the presence of Q waves in the leads of the ST-segment elevation nor a history of a previous myocardial infarction in a different location disqualified the patient from entry into the study. Other exclusion criteria were applied as described previously.[15]

After informed consent was obtained, each patient received 5,000 IU of heparin intraarterially and 100 mg of aspirin by mouth at the beginning of cardiac catheterization. The perfusion status of the infarct-related coronary artery was classified according to the grading system of the Thrombolysis in Myocardial Infarction (TIMI) study.[16] Eligible patients only entered the trial after the attending cardiologist had determined that the infarct-related coronary artery remained occluded (TIMI grade 0) after intracoronary administration of 200 μg of nitroglycerin.

Patients with a body weight <90 kg were given 70 mg of alteplase (Actilyse®, donated by Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) intravenously in 1 to 3 minutes; an 80-mg bolus was given to patients weighing ≥90 kg. The status of the infarct-related coronary artery was checked angiographically in all patients 60 and 90 minutes later. After the 90-minute angiography, further therapeutic maneuvers, such as percutaneous transluminal coronary angioplasty, were performed at the discretion of the attending cardiologist. If the TIMI grade of the infarct-related coronary artery at the 90-minute coronary angiography was 2 (partial perfusion) or 3 (complete perfusion), and if no instrumental or surgical coronary intervention was required at that time, the patient was randomized to receive immediately either a second intravenous bolus of alteplase (30 mg in 1 to 3 minutes) or an intravenous infusion of alteplase (30 mg over 3 hours). At the same time, a maintenance infusion of heparin (1,000 IU/hour) was begun in randomized patients and was continued until the last angiogram was obtained 12 to 24 hours after the start of thrombolytic treatment. All coronary angiograms were also read by an independent cardiologist, without knowledge of the treatment given. For this report, core laboratory readings were used and TIMI grades 2 and 3 were considered to indicate patent arteries. For patients who were not randomized, the 90-minute angiography was the end point of the study. Adverse events were reported until the time of hospital discharge. Mortality was evaluated 14 days after the administration of trial treatment. In the first 12 to 24 hours of the study, antiplatelet agents, other than aspirin, were not allowed.

Laboratory assays: For the assay of plasma fibrinogen, blood samples were collected on sodium citrate (final concentration 0.01 M) containing aprotinin (Trasylol®; Bayer, Leverkusen, Germany) (final concentration 150 KIU/ml) before and 90 and 270 minutes after the start of thrombolytic treatment. Fibrinogen was measured by the methods of Ratnoff and Menzie[17] and Clauss.[18] Plasma lipoprotein (a) [Lp(a)] was quantified with the biopool TintElize™ Lp(a) enzyme immunoassay (Biopool AB, Umeå, Sweden).

Statistics: Exact 95% confidence intervals of proportions were calculated according to the method described by Armitage and Berry.[19] The statistical calculations were performed using the statistical package SAS.[20] Unless stated otherwise, data are given as mean ± standard deviation.

RESULTS

Sixty patients (78% men) entered the study between the beginning of September 1989 and the end of April 1990. All but 2 patients were treated for their first

acute myocardial infarction at a mean of 230 ± 53 minutes (range 90 to 300) after symptom onset. At central reading of the pretreatment angiograms, the TIMI grade of the infarct-related coronary artery was 0 before and after intracoronary administration of nitroglycerin in all but 2 patients whose arteries were TIMI grade 1 after nitroglycerin. Nine patients had a body weight ≥90 kg and received a bolus dose of 80 mg of alteplase. The perfusion status of the infarct-related coronary artery was grade 2 in 10 patients (17%), grade 3 in 23 patients (38%) at 60 minutes, grade 2 in 7 patients (12%), and grade 3 in 22 patients (37%) at 90 minutes. This corresponds to a patency rate of 55% (95% confidence interval, 43 to 66%) at 60 minutes and of 48% (95% confidence interval, 37 to 60%) at 90 minutes.

Patients with recanalized infarct-related coronary artery at 90 minutes: The further treatment and angiographic outcome of the 29 patients with a patent infarct-related coronary artery during 90-minute angiography are shown in Figure 1. In 6 (5 with TIMI grade 2 and 1 with TIMI grade 3 at 90-minute angiography), percutaneous transluminal coronary angioplasty was performed at once and was successful in all. The remaining 23 patients with a patent infarct-related coronary artery at 90 minutes received at random either a second bolus of alteplase (30 mg, 12 patients) or an infusion of alteplase (30 mg in 3 hours, 11 patients). Randomized patients also received a continuous intravenous infusion of heparin (1,000 IU/hour) between the angiographies performed at 90 minutes and those performed at 12 to 24 hours; however, in 2 patients randomized to alteplase infusion, heparin infusion was either not begun or prematurely discontinued after 6 hours because of puncture site bleeding. In 2 patients, randomized to alteplase infusion, control angiography was delayed for 25 and 31 hours, respectively, for technical reasons. At this final angiography, perfusion grade 3 was present in 22 of the randomized patients. In 1 patient with TIMI grade 3 at 90-minute angiography and who subsequently received an infusion of alteplase, the infarct-related coronary artery had reoccluded (TIMI grade 0) by the time of the control angiography at 31 hours; in this patient the infusion of heparin had been prematurely discontinued. The angiographic reocclusion rate at 12 to 24 hours was thus 4%.

Patients with occluded infarct-related coronary artery at 90 minutes: At 90 minutes, the infarct-related coronary artery was closed in 31 patients (2 with TIMI grade 1, 29 with TIMI grade 0). In 22 of them (1 with TIMI grade 1 and 21 with TIMI grade 0), percutaneous transluminal coronary angioplasty was performed immediately and was successful in 16 patients, all with TIMI grade 0 at 90 minutes (Figure 1).

Adverse events and mortality: There was no major bleeding; minor hemorrhagic complications were observed in 65% (95% confidence interval, 53 to 75%) of patients and they occurred primarily at puncture sites (48% of all patients [95% confidence interval, 37 to 60%]). No patient required a blood transfusion. All patients were alive 2 weeks after thrombolytic treatment.

Plasma fibrinogen and lipoprotein (a): Plasma fibrinogen was assessed both with the method of Ratnoff and Menzie[17] and with the clotting rate assay of Clauss,[18] in samples obtained in 54 patients, before, and 90 and 270 minutes after bolus administration of alteplase. With the former method, fibrinogen levels were 2.74 ± 0.56, 1.59 ± 0.85 and 1.64 ± 0.84 g/liter at the aforementioned time points, respectively; corresponding values obtained with the latter method were 2.85 ± 1.04, 0.77 ± 0.73 and 1.01 ± 1.06 g/liter, respectively.

Median (range) Lp(a) levels before, and 90 and 270 minutes after thrombolytic treatment were 161.5 mg/liter (0 to 1,422), 170.5 mg/liter (0 to 1,440) and 202 (4 to 1,776) mg/liter, respectively. The median values (ranges) of Lp(a) at baseline were 166 (10 to 1,128) and 155 (0 to 1,422) mg/liter in patients with

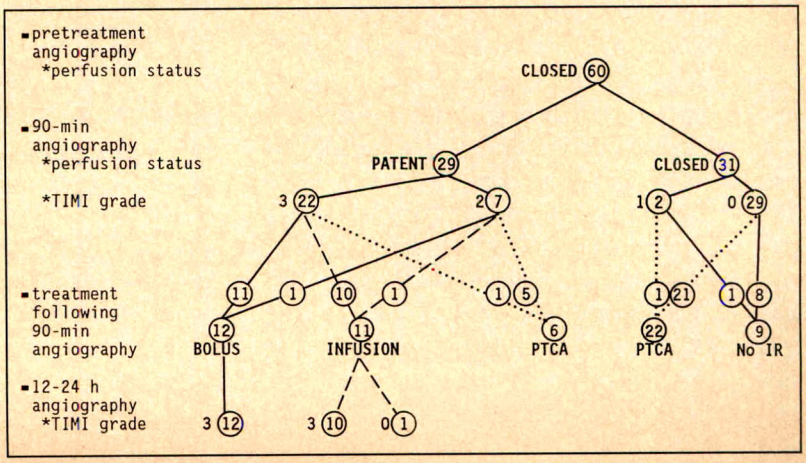


FIGURE 1. Flow diagram for angiographic outcome and treatment. Numbers of patients are within *circles*. IR = coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; TIMI= Thrombolysis in Myocardial Infarction trial.

and without a recanalized infarct-related coronary artery at 90 minutes, respectively. The recanalization rate at 90 minutes was 56% in 18 patients with Lp(a) level at baseline ≥300 mg/liter and was 45% in 42 patients with Lp(a) level at baseline <300 mg/liter. Logistic regression analysis with recanalization as the response variable (i.e., reperfusion [TIMI grades 2 and 3] or no reperfusion [TIMI grades 0 and 1]) and baseline Lp(a) levels, or baseline Lp(a) levels squared, as the explanatory variable, revealed that Lp(a) is not significantly related to reperfusion ($p = 0.6133$ and $p = 0.1435$, respectively).

DISCUSSION

Clinical experience with a bolus administration of alteplase in acute myocardial infarction is still limited. Tebbe et al[11] observed a patency rate of 75% in 20 patients 60 minutes after a single bolus injection of 50 mg single-chain rt-PA (alteplase). Khan et al[12] found a recanalization rate at 90 minutes of 79% in 14 patients after 4 bolus injections of 10 clot-lysis megaunits of double chain rt-PA at 20-minute intervals. In our previous trial with single-chain rt-PA (alteplase), recanalization rates of 72% (confidence interval, 54 to 89%), 32% (confidence interval, 15 to 49%) and 45% (confidence interval, 27 to 63%) were obtained 60 minutes after a single bolus injection of 70, 60 and 50 mg of alteplase, respectively.[13] Although the 70-mg bolus dose gave the best results in our pilot study, in the present trial we obtained a recanalization rate of 48% (confidence interval, 37 to 60%) at 90 minutes, which is distinctly lower but not contradictory to our previous findings because the confidence intervals overlap.

The observed recanalization rate in the present trial is also lower than that obtained by Mueller et al[2] at the end of an intravenous infusion of 70 mg alteplase over 90 minutes (71% [95% confidence interval, 61 to 81%]).[2] In the TIMI I trial,[16] recanalization (TIMI grades 2 or 3) was observed in 62% (70 of 113) of patients with TIMI grade 0 or 1 perfusion at baseline, 90 minutes after initiation of intravenous administration of 80 mg of 2-chain rt-PA (40, 20 and 20 mg in successive hours). In the same study, the patency rate at 90 minutes, including the patients with patent infarct-related coronary arteries (TIMI grade 2 or 3) at baseline (21% of all patients assigned to rt-PA), was 70% (100 of 143) in the rt-PA group.[21] If one assumes that in approximately 20% of patients the infarct-related coronary artery is patent (TIMI grade 2 or 3) at baseline, the recanalization rate of 48% in the present study may correspond to a patency rate of approximately 58%. This is again lower than the observed patency rates of 69% (84 of 121)[22] and 75% (98 of 131)[23] at approximately 90 minutes, and the estimated patency rate of 89% at 90 minutes[24] obtained after administration of 70 mg of single-chain rt-PA in various dosage regimens, all comprising an initial bolus of 6 to 10 mg, followed by a continuous intravenous infusion. Even a patency rate of 91% has been observed at the end of a front-loading intravenous infusion of 100 mg of alteplase over 90 minutes in 74 patients (15 mg initial bolus, 50 mg infusion over 30 minutes and 35 mg infusion over the next 60 minutes).[25]

Lp(a) is assembled from low-density lipoprotein and apolipoprotein (a). Apolipoprotein (a) is homologous to plasminogen because it contains a plasminogen-like serine protease domain and 2 types of plasminogen-like kringle domains. Because of this high degree of homology to plasminogen it was suggested that Lp(a) may interfere with fibrinolysis through its competition with plasminogen for binding on fibrin or on endothelial cells, or both.[26] Our data indicate that raised Lp(a) levels do not adversely affect coronary recanalization with alteplase and are in agreement with similar observations by Armstrong et al[27] in thrombolytic treatment with saruplase (pro-urokinase).

Fibrinogenolysis was less pronounced when fibrinogen was assayed with the method of Ratnoff and Menzie,[17] which measures total clottable protein, than with the Clauss method,[18] which is based on the rate of coagulation and measures rapidly coagulable fibrinogen but not slowly coagulable early degradation products of fibrinogen. This finding is in accordance with previous reports.[28,29]

In conclusion, 70 mg of alteplase, administered as a bolus dose, is associated with a lower recanalization rate than the same dose administered over 90 minutes. An accelerated infusion of the usual dose of 100 mg alteplase over 90 minutes rather than over 3 hours results in the highest patency rates at 90 minutes thus far reported with any thrombolytic drug.

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Older Age and Elevated Blood Pressure are Risk Factors for Intracerebral Hemorrhage After Thrombolysis

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Intracerebral hemorrhage is an important concern after thrombolytic therapy for acute myocardial infarction, but risk factors are controversial. Accordingly, we assessed risk factors in 107 treated patients of whom 4 had intracerebral hemorrhage. Intracerebral hemorrhage occurred at a mean of 25 hours (range 3.5 to 48) after therapy and was fatal in 2 patients. Significant differences were found between patients with and without intracerebral hemorrhage for age (77 ± 7 vs 62 ± 11 years, p ≤0.01), and initial (161 ± 23 vs 135 ± 23 mm Hg, p ≤0.03) and maximal (171 ± 30 vs 146 ± 20, p ≤0.02) systolic blood pressures. Initial and maximal diastolic blood pressures also tended to be higher (101 ± 25 vs 86 ± 16, p ≤0.07; 104 ± 24 vs 90 ± 13, p ≤0.06). Differences did not achieve significance for comparisons of gender, height, weight, site of infarction, time to therapy, specific thrombolytic agent used, concomitant therapy, interventions and partial thromboplastin time. It is concluded that age (≥70 years) and elevated blood pressure (≥150/95 mm Hg) are important risk factors for intracerebral hemorrhage. The overall balance of benefit and risk of thrombolysis should continue to be assessed by large mortality trials.

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Thrombolysis is now accepted therapy for acute myocardial infarction.[1–7] However, its adverse potential remains of concern.[8–16] Intracerebral hemorrhage represents the most serious potential adverse reaction.[8–16] Although relatively uncommon, it is a devastating event, being fatal in about one-half of patients and causing significant disability in most survivors.[15] Several risk factors have been proposed,[9–15] but these remain controversial.[16] Some of the proposed risk factors include a history of stroke (especially if hemorrhagic), advanced age, systemic hypertension, female gender, the use of aspirin, and excessive doses of thrombolytic agents or of concomitant heparin. This study identifies factors in our hospital by comparing characteristics among a series of consecutive patients with acute myocardial infarction receiving thrombolytic therapy who did and did not have intracerebral hemorrhage.

METHODS

Patients: Patients were identified by a computerized record search of hospital admissions between January 1987 and 1990. (The LDS Hospital uses the HELP data base program operating on a Tandem computer system.) All discharge diagnoses of acute myocardial infarction were sought for patients admitted to the hospital. Those that had received an intravenous thrombolytic agent were entered into the study. Among these, every stroke and intracranial hemorrhagic event was identified and verified by investigator review of the medical record.

Characteristics of myocardial infarction patient group. In all, 107 consecutive patients initially admitted to LDS Hospital and receiving thrombolytic therapy for acute myocardial infarction were identified. Patient characteristics are summarized in Table I. Average age was 63 years, and most were men. Site of infarction was anterior in one-third and inferior or other location in two-thirds of patients. Time to therapy averaged 4 hours. Most received either streptokinase or alteplase, with a few receiving anistreplase or urokinase.

At the time of myocardial infarction, a minority (between 10 and 18%) were taking β blockers, calcium

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antagonists, aspirin or nitrates. During hospitalization, β blockers were used in 37%, calcium blockers in 53%, aspirin in 79%, and heparin and nitrates in >90%.

Characteristics of patients with intracerebral hemorrhage: In this series, 4 patients with intracerebral hemorrhage were identified. The high rate of 4% in our series prompted further analysis of risk factors. Characteristics of these 4 are listed in Table II. The frontal lobe was involved in all cases, with more extensive involvement in 2. Two died and 2 showed residual disability. Representative computed tomography scans, available for 3 patients, are shown in Figure 1.

Proposed risk factors and statistical approach: Before the computer search was initiated, characteristics of interest were identified that might be associated with risk of intracerebral hemorrhage. Because multiple comparisons were anticipated, a limited number of variables of primary interest were prospectively defined, based on published reviews[8–16] and our index case. These included age and systolic blood pressure. Additional variables of interest included diastolic blood pres-

TABLE I Demographic Characteristics

No. of study patients	107
Age (yr) (mean ± SD)	63 ± 11
Gender, n (%)	
Men	83 (78%)
Women	24 (22%)
Site of myocardial infarction, n (%)	
Anterior	37 (35%)
Inferior	69 (65%)
Time to therapy (mean ± SD, hours)	4.0 ± 2.5
Thrombolytic drugs, n (%)	
Streptokinase	57 (53%)
Alteplase	37 (34%)
Anistreplase	11 (11%)
Urokinase	2 (2%)
Medications at time of myocardial infarction, n (%)	
β blockers	12 (11%)
Calcium antagonists	15 (14%)
Aspirin	19 (18%)
Nitrates	11 (10%)
Concomitant medications, n (%)	
β blockers	40 (37%)
Calcium antagonists	57 (53%)
Aspirin	84 (79%)
Heparin	99 (93%)
Nitrates	101 (94%)

SD = standard deviation.

TABLE II Characteristics of Patients with Intracerebral Hemorrhage (n = 4)

	Patient Number			
	1	2	3	4
Gender	Men	Men	Women	Women
Initial blood pressure (mm Hg)	138/88	162/89	192/138*	152/90
Age (yr)	72	74	87	73
Thrombolytic drug	tPA	SK	tPA	SK
Time to therapy (hours)	2.5	4	6.5	4
Time of ICH from therapy (hours)	3.5	48	42.5	9
PTT max	>130	>130	>130	>130
PTT before ICH	29	94	46	127
Outcome	Died	Disabled	Disabled	Died

*Treatment given after normalization of pressures.
ICH = intracerebral hemorrhage; max = maximum; PTT = partial thromboplastin time; SK = streptokinase; tPA = tissue plasminogen activator.

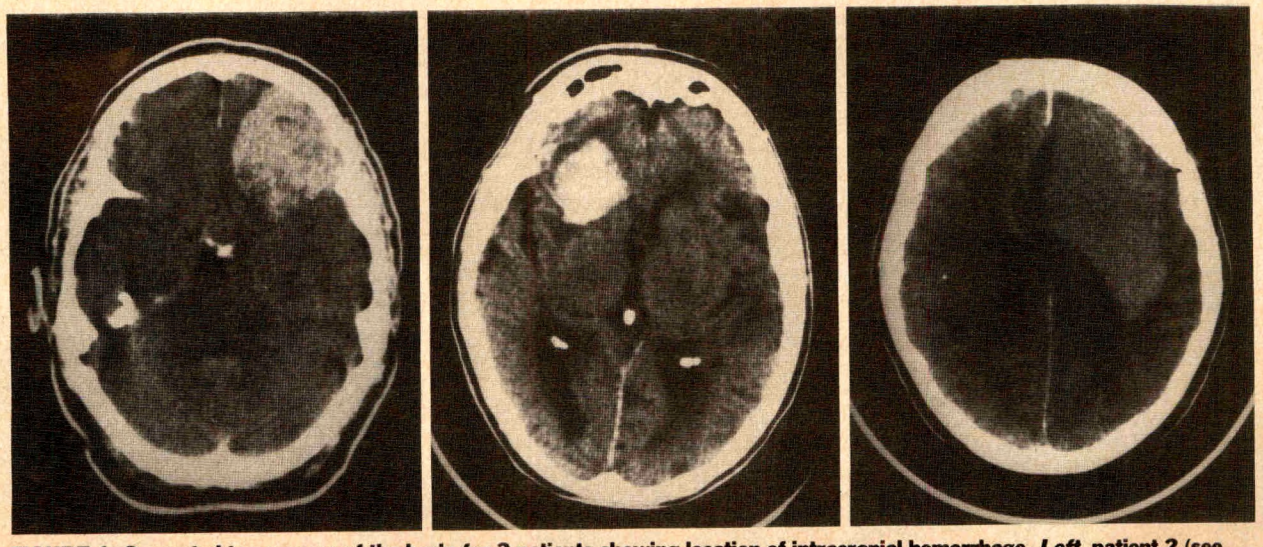


FIGURE 1. Computed tomograms of the brain for 3 patients showing location of intracranial hemorrhage. *Left*, patient 2 (see Table II) (L-frontal hematoma); *middle*, patient 3 (R-frontal hematoma); *right*, patient 4 (L-frontoparietal hematoma).

TABLE III Comparisons Between Patients With and Without Intracerebral Hemorrhage

Variables	With ICH (n = 4)	Without ICH (n = 103)	p Value
Age (years)	77 ± 7 (72–87)	63 ± 11 (33–88)	0.01
Systolic blood pressure			
Initial	161 ± 23	135 ± 23	0.03
Maximal	171 ± 30	146 ± 20	0.02
Diastolic blood pressure			
Initial	101 ± 25	86 ± 16	0.07
Maximal	104 ± 23	90 ± 13	0.06
Gender, n (%) women	2	22 (21%)	0.20
Height (cm)	158 ± 22	172 ± 13	0.08
Weight (kg)	83 ± 39	83 ± 20	0.96
Time to therapy,	229 ± 106	237 ± 151	0.91
Partial thromboplastin time maximum (sec)	>130	114 ± 30	0.33

Values are mean ± standard deviation. Age also includes range.
ICH = intracerebral hemorrhage.

sure, gender, thrombolytic agent and partial thromboplastin time.

Student's unpaired *t* test was used for between-group comparisons of continuous variables and chi-square or Fisher's exact test for comparisons of categorical variables. A p value <0.05 (2-tailed) was considered significant for the primary variables. Because of the multiple comparisons, a p value for the other variables of <0.05 was considered only suggestive, whereas a value <0.01 for these other comparisons was considered significant.

RESULTS

Age, hypertension and risk of intracerebral hemorrhage: A comparison of age showed a significant difference between groups with (n = 4) and without (n = 103) intracerebral hemorrhage (p ≤0.01) (Table III). Mean age ± standard deviation (range 72 to 87) was 77 ± 7 years in patients with intracerebral hemorrhage compared with 63 ± 11 years in the remaining treated patients.

Blood pressure comparisons between the 2 groups also showed significant differences, especially for systolic pressure (Table III; Figure 2). Initial systolic pressure (first measurement obtained on admission) averaged 161 mm Hg in the group with cerebral hemorrhage, compared with 135 mm Hg in the other patients (p ≤0.03), and the maximal systolic blood pressures subsequently recorded averaged 171 and 146 mm Hg, respectively (p ≤0.02). Diastolic blood pressures also tended to be higher in the group with intracerebral hemorrhage (mean initial readings 101 vs 86 mm Hg, and the subsequent maximal readings 104 vs 90), although these differences did not achieve significance.

Individual data points relating systolic blood pressure and age for the entire group are shown in Figure 3. The odds ratios for age and blood pressure as risk factors are shown in Figure 4. Age was dichotomized at 70 years, systolic blood pressure at 150 mm Hg and diastolic blood pressure at 95 mm Hg, using receiver operator curve analysis, and odds ratios computed together with 95% confidence intervals. Because of the small numbers, the 95% confidence intervals are broad; the odds ratio for age ≥70 years is 26, but the lower confidence bound extends to 1.8. The odds ratios for systolic blood pressure ≥150 mm Hg are 8 for initial and 16 for maximal readings, but the confidence intervals indicate that they may be as low as about 1. Odds

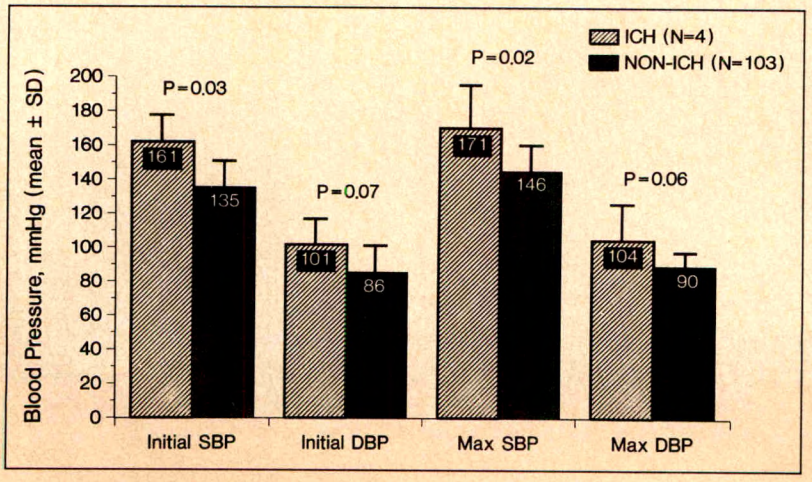


FIGURE 2. Blood pressure comparisons between groups with *(shaded bars)* and without *(black bars)* intracerebral hemorrhage (ICH). DBP = diastolic blood pressure; Max = maximal recorded blood pressure after initial reading; NON-ICH = without intracerebral hemmorrhage; SBP = systolic blood pressure; SD = standard deviation.

ratios for diastolic blood pressure ≥95 mm Hg are 2 to 3, but confidence intervals overlap the line of identity.

Other baseline factors and risk: Differences in other characteristics of interest as possible risk factors between the 2 groups are listed in Table III. Two of 4 patients with intracerebral hemorrhage (50%) were women, versus 21% of other patients, but the difference was not significant. Similarly, intergroup differences in height, weight, time to therapy, site of myocardial infarction (2 anterior, 2 inferior), and maximal partial thromboplastin time were not significant.

Medication and risk: Intracerebral hemorrhage followed administration of streptokinase and alteplase each in 2 patients. This distribution of thrombolytic drugs was not significantly different from that of the overall distribution used for myocardial infarction (Tables I and IV).

Other medications used at home before hospitalization as well as concomitant medications given in the hospital are listed and compared in the 2 groups in Table IV. There were no significant differences in home (before the hospital) medication use for β-blockers, calcium channel blockers, aspirin and nitrates. In the hospital, there were also no differences in the concomitant use of β-blockers, calcium blockers, heparin and nitrates. There was a nominal difference in hospital use of aspirin that may have been due to chance or to selection bias; e.g., aspirin would have been withheld from those who experienced early intracerebral hemorrhage.

TABLE IV Medications Used in Patients With and Without Intracerebral Hemorrhage

	With ICH (n = 4)	Without ICH (n = 103)	p Value
Thrombolytic drugs, n (%)			
Streptokinase	2 (50%)	55 (53%)	0.71
Alteplase	2 (50%)	35 (34%)	0.90
Anistreplase	0 (0%)	11 (11%)	0.88
Urokinase	0 (0%)	2 (2%)	0.11
Home medications, n (%)			
β blockers	2 (50%)	10 (10%)	0.09
Calcium antagonists	0 (0%)	15 (15%)	0.93
Aspirin	0 (0%)	19 (18%)	0.78
Nitrates	1 (25%)	11 (11%)	0.93
Concomitant medications, n (%)			
β blockers	1 (25%)	39 (38%)	0.99
Calcium antagonists	2 (50%)	55 (53%)	0.71
Aspirin	1 (25%)	83 (79%)	0.04
Heparin	3 (75%)	95 (92%)	0.69
Nitrates	4 (100%)	97 (94%)	0.54

DISCUSSION

Study summary: This study suggests that older age (especially ≥70 years) and systemic hypertension (especially systolic blood pressure ≥150 mm Hg), even if transient on presentation, are significant risk factors for intracerebral hemorrhage in patients with acute myocardial infarction who are treated with thrombolytic agents. Other risk factors may also be important, but require additional study.

Study limitations: Limitations of this study include its retrospective nature, raising the possibility of ascertainment bias, and the small number of patients with an event, reducing the power of the observations and increasing the chance of spurious findings. For example, the significance of age may have disappeared if only 1 or 2 more events in much younger patients had occurred. Thus, these results should be compared with other series to see whether they are replicated. Combining several smaller trails into an overview (metanalysis) may also reinforce these results.

Previously published studies: In a Seattle series,[13] 3 intracerebral hemorrhagic events occurred among 160 patients given alteplase, an incidence of 1.9%. Consistent with our own study results, both initial systolic and diastolic hypertension, even though transient, were risk

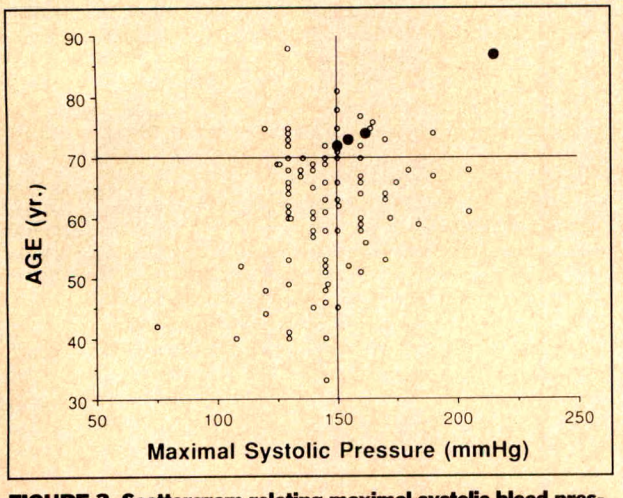


FIGURE 3. Scattergram relating maximal systolic blood pressure recording *(abscissa)* with age *(ordinate)*. Patients experiencing intracerebral hemorrhage are denoted by *larger, closed circles*, others by *open circles*. Note clustering of events in quadrant of values for age ≥70 years and systolic blood pressure ≥150 mm Hg.

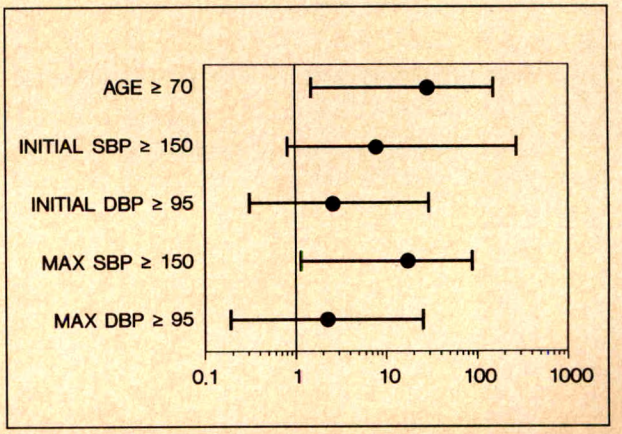


FIGURE 4. Risk of intracerebral hemorrhage for age ≥70 years, and initial and maximal (MAX) systolic blood pressures (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥95 mm Hg; values are odds ratios with 95% confidence intervals.

factors in a preliminary analysis. Taking aspirin on admission was an additional risk factor.

In the recent United States study of Kase et al,[11] 3 of 60 patients and an additional 3 referred patients had intracerebral hemorrhage after receiving alteplase and heparin, and 4 of these died. The prothrombin time was >80 seconds in all 6 and was >150 seconds in 4.

In the Second Thrombolysis in Myocardial Infarction study experience,[14,15] high-dose alteplase (150 mg) was associated with an unacceptable intracranial hemorrhage rate of 1.5%. After a reduction in dose to 100 mg, risk was reduced to 0.5%. Additional analyses have recently been published from this trial, in which 23 intracerebral hemorrhages (48% fatal) occurred among 3,996 patients treated with alteplase.[15] Consistent with the findings of the present study, older age ($p < 0.001$) and elevated blood pressure (systolic >180 mm Hg or diastolic >110 mm Hg) ($p < 0.012$) were associated with an increased risk of intracerebral hemorrhage. The possibility of therapy with β blockers decreasing risk and calcium antagonists increasing risk was also raised.

In contrast to these studies, O'Connor et al,[16] reporting for the Thrombolysis and Angioplasty in Myocardial Infarction group, could not identify specific risk factors for intracerebral hemorrhage.

Large mortality studies[2,4,6,17] have documented the relative risk of stroke from all causes in treated and untreated patients, but they have often not reported on, or may have incomplete ascertainment for, intracerebral hemorrhage and for the association of baseline variables with intracerebral hemorrhagic events. Because thrombolytic therapy may decrease thromboembolic stroke while increasing intracerebral hemorrhage, the effect of baseline characteristics, which have not always been completely documented, specifically on intracerebral hemorrhage may be obscured in these large studies. Fortunately, in patients with well-accepted indications for therapy, the rate of all-cause stroke appears to be approximately the same or only slightly increased in treated and untreated patients, at least in some study populations and for some thrombolytic regimens.[2,4,6]

We conclude that older age and elevated initial blood pressure are risk factors for intracerebral hemorrhage after thrombolysis. The overall balance of benefit and risk of thrombolysis should continue to be assessed by large mortality trials. Knowledge of risk factors may aid in decision-making in individual cases.

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Early Prediction of Acute Myocardial Infarction from Clinical History, Examination and Electrocardiogram in the Emergency Room

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The possibility of early prediction of acute myocardial infarction (AMI) was assessed in 7,157 consecutive patients coming to our emergency room during a 21-month period with chest pain or other symptoms suggestive of AMI. Of these patients 921 developed an AMI during the first 3 days in the hospital. Of the 4,690 patients admitted to hospital, 1,576 (34%) had a normal admission electrocardiogram, and 90 of these (6%) developed AMI. Of 1,964 patients with an abnormal electrocardiogram without signs of acute ischemia (42% of those admitted), 268 (14%) developed AMI, and 563 (51%) of 1,109 patients with acute ischemia on the electrocardiogram (24%) developed AMI. All patients were prospectively classified in the emergency room on the basis of history, clinical examination and electrocardiogram into 1 of 4 categories, according to the initial degree of suspicion of AMI. Of 279 admitted patients judged to have an obvious AMI (6% of the 4,690), 245 (88%) actually developed AMI; of 1,426 with a strong suspicion of AMI (30%), 478 (34%) developed one; of 2,519 with a vague suspicion of AMI (54%), 192 (8%) developed one; and of 466 with no suspicion of AMI (10%), 6 (1%) developed one. Thus, only a low percentage of the patients with a normal initial electrocardiogram or a vague initial suspicion of AMI developed a confirmed AMI.

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Many patients come to the emergency room of every hospital with chest pain or other symptoms suggestive of acute myocardial infarction (AMI). Only a minority of these patients develop a confirmed AMI. Most of the patients judged sufficiently likely in the emergency room to have an AMI are admitted to a coronary care unit, but only 16 to 50% of them actually develop a confirmed AMI.[1–7] Although many of the patients do not develop an AMI, they are not necessarily admitted needlessly, since they may have unstable angina pectoris, severe heart failure, arrhythmias, or other symptoms requiring treatment in a coronary care unit. However, there is great interest in the early prediction of infarction in order to be able to select high-risk patients for immediate intensive care. The possibility of early intervention aimed at myocardial salvage, especially with thrombolytic agents, further underlines the importance of early diagnosis. This study describes our experience with predicting development of AMI in consecutive, unselected patients presenting to the emergency room of a single hospital with chest pain or other symptoms suggestive of AMI.

METHODS

Patients: Sahlgrenska Hospital, Göteborg, Sweden, serves a population of about 230,000. All patients presenting to the emergency room between February 15, 1986, and November 9, 1987, with chest pain or other symptoms suggestive of AMI were consecutively registered.

A full history was taken, including details of previous AMIs and angina pectoris.

A standard 12-lead electrocardiogram was registered soon after admission to the emergency room and classified the following day into 1 of the following groups by an experienced member of our study group: (1) normal (no pathologic signs); (2) pathologic but no signs of acute ischemia (e.g., old infarction, bundle branch block, nonspecific ST-T changes); (3) signs of acute ischemia (ST elevation $\geq$1 mm in leads aVL, aVF, I, II, III, V_5-V_6 or $\geq$2 mm in leads V_1-V_4; ST depression $\geq$1 mm; T-wave inversion; Q wave $\geq$2 mm deep) in $\geq$2 leads. Thus, the attending doctor did not

TABLE I Final Diagnosis During First Three Days in the Hospital in Relation to Initial Suspicion of AMI in 4,690 Patients

	Categories				
	1 (n = 279)	2 (n = 1,426)	3 (n = 2,519)	4 (n = 466)	Total (n = 4,690)
Confirmed AMI	245	478	192	6	921
Q-wave AMI	203	175	34	1	413
Possible AMI	14	163	171	8	356
Myocardial ischemia	9	172	225	13	419
Possible myocardial ischemia	5	478	752	56	1,291
Diagnosis other than myocardial ischemia	1	80	261	48	390
Discharged within 1 day with no suspicion of AMI	5	55	913	335	1,308
Diagnosis missing	0	0	5	0	5

AMI = acute myocardial infarction.

classify the electrocardiogram for the study, and his treatment of the patient was independent of the official study classification.

Based on history, clinical examination, and standard 12-lead electrocardiogram recorded soon after admission to the emergency room, all patients were prospectively classified by the doctor on duty into 4 categories depending on the degree of initial suspicion of AMI: (1) obvious AMI — typical symptoms, and ST elevation with or without Q waves on the initial 12-lead electrocardiogram; (2) strong suspicion of AMI, which included subcategories — a, typical symptoms, but an electrocardiogram without ST elevation or Q waves, b, atypical symptoms, but ST-T changes or Q waves on the electrocardiogram, c, sudden onset of severe congestive heart failure without ST elevation on the electrocardiogram, and d, unstable angina pectoris regardless of electrocardiogram; (3) vague suspicion of AMI — difficulties in the interpretation of the symptoms and no signs of acute ischemia on the electrocardiogram; and (4) no suspicion of AMI — a, no suspicion of coronary artery disease, and b, stable angina pectoris.

For the subsequent diagnosis of a confirmed AMI, 2 of the following criteria had to be fulfilled: (1) chest pain with a duration of ≥15 minutes, (2) serum aspartate aminotransferase above the normal range in samples from ≥2 different days, and (3) appearance of new Q waves in ≥2 leads on a 12-lead standard electrocardiogram. For the diagnosis of a possible AMI, chest pain and at least 1 of the following criteria had to be present: (1) 1 serum aspartate aminotransferase above the normal range, or 1 creatine kinase above the normal range; and (2) appearance of a new Q wave in only 1 lead of a 12-lead standard electrocardiogram. For the diagnosis of myocardial ischemia, at least 1 of the following signs of ischemia had to be present in ≥2 leads of a 12-lead standard electrocardiogram (without elevations of serum aspartate aminotransferase or creatine kinase): (1) ST depression of ≥1 mm, (2) ST elevation of ≥1 mm, or (3) T-wave inversion. For the diagnosis of possible myocardial ischemia, there had to be a clinical suspicion of myocardial ischemia, but no electrocardiographic signs of ischemia.

RESULTS

Of the 7,157 patients who came to the emergency room with chest pain or other symptoms suggestive of AMI during the study, 4,690 (66%) were admitted to hospital, with 2,223 (31%) being primarily admitted to the coronary care unit.

Diagnosis in relation to initial suspicion of acute myocardial infarction. Of the 4,690 patients admitted to the hospital, 279 (6%) were considered to belong to category 1, 1,426 (30%) to category 2, 2,519 (54%) to category 3, and 466 (10%) to category 4. Of the total study population of 7,157 patients seen in the emergency room, 284 (4%) were considered to belong to category 1, 1,431 (20%) to category 2, 2,532 (35%) to category 3, and 2,910 (41%) to category 4.

Table I lists the diagnoses made during the first 3 days in the hospital in relation to initial degree of suspicion of AMI. Among patients considered to have an obvious AMI in the emergency room, 88% actually developed a confirmed AMI during the first 3 days in the hospital. This figure was higher in patients without (93%) than with (81%) a previous history of coronary artery disease. (The percentages in relation to previous history of coronary artery disease are not listed in the tables.) Among patients classified into category 2 (i.e., strong suspicion of AMI), 34% developed a confirmed AMI. Also, this figure was somewhat higher in patients without (37%) than with (32%) a previous history of coronary artery disease. In patients judged to have a vague suspicion of AMI (category 3), 8% developed a confirmed AMI. There was no difference between patients with (8%) or without (7%) a history of previous AMI or angina. In category 4 (the patients considered to have no suspicion of AMI), 1% developed a confirmed AMI.

Most of the patients who developed a confirmed AMI (52%) were classified into category 2. Although the percentage of patients developing infarction was

TABLE II Number of Patients with Different Admission Electrocardiographic Patterns in Relation to Initial Suspicion of AMI and Number Developing AMI in 4,690 Patients Admitted to the Hospital

	Categories				
	1— Obvious AMI (n = 279)	2— Strong Suspicion of AMI (n = 1,426)	3— Vague Suspicion of AMI (n = 2,519)	4— No Suspicion of AMI (n = 466)	Total (n = 4,690)
Normal ECG*	4 (2)	300 (50)	1,047 (37)	225 (1)	1,576 (90)
Pathologic ECG* but no acute ischemia	16 (6)	649 (167)	1,118 (91)	181 (4)	1,964 (268)
Acute ischemia* on ECG	259 (237)	474 (261)	328 (64)	48 (1)	1,109 (563)
ST elevation†	232 (216)	165 (136)	52 (15)	15 (1)	464 (368)
ST depression†	90 (81)	235 (116)	135 (32)	14 (0)	474 (229)
T-wave inversion†	45 (40)	155 (73)	165 (27)	23 (0)	338 (140)
Q wave†	94 (90)	56 (47)	13 (5)	2 (0)	165 (142)

*Information is missing in 50 patients.
†Information is missing in 72 patients.
Numbers in parentheses are the patients who developed acute myocardial infarction during first 3 days in the hospital.
AMI = acute myocardial infarction; ECG = electrocardiogram.

much higher in category 1, only 27% of all infarctions were in this category. Because of the large number of patients in category 3, almost as many infarctions developed in this category (21% of total) as in category 1.

Infarct development in relation to initial suspicion of acute myocardial infarction and admission electrocardiogram (Table II): A normal initial electrocardiogram in the emergency room was registered for 1,576 of the patients (34%) admitted to the hospital. One percent of the patients in category 1, 21% in category 2, 42% in category 3 and 49% in category 4 had normal electrocardiograms. Abnormal electrocardiograms but without signs of acute ischemia were found in 1,964 of admitted patients (42%), with almost similar percentages being found in categories 2, 3 and 4. Signs of acute myocardial ischemia on the electrocardiogram were present in 1,109 of all patients admitted (24%), with ST elevation in 10%, ST depression in 10%, T-wave inversion in 8% and Q waves in 4% (these figures add up to >24, because some of the electrocardiograms showed >1 sign of acute ischemia). Ninety-three percent of patients in category 1, 33% in category 2, 13% in category 3 and 11% in category 4 had acute ischemia on the electrocardiogram.

For example, of 1,576 patients with a normal electrocardiogram, 90 (6%) developed an AMI, a figure that was higher in patients with (8%) than without (4%) a history of coronary artery disease. Among 1,964 patients with an abnormal electrocardiogram but with no signs of acute ischemia, 268 (14%) developed a confirmed AMI. In these patients, infarct development did not differ between those with and without a history of ischemic heart disease (14%). Among 1,109 patients with signs of acute ischemia on the electrocardiogram, 563 (51%) developed a confirmed AMI. The proportion was highest in patients with Q waves (86%), followed by ST elevation (79%), ST depression (48%) and T-wave inversion (36%). An AMI developed more often in men (56%) than in women (42%) for all types of acute ischemia on the initial electrocardiogram (not listed in the Table). Some patients had >1 type of electrocardiographic abnormality. Eighty-nine of 258 patients with only ST depression (34%) and 53 of 186 with only T-wave inversion (28%) developed AMI.

Ten percent of all AMIs were diagnosed in patients with a normal electrocardiogram on admission, 29% in patients with a pathologic electrocardiogram but without acute ischemia, and 61% in patients whose electrocardiogram showed acute ischemia.

In patients with a normal admission electrocardiogram, 50% of the patients in category 1, 17% of those in category 2, 4% of those in category 3 and 0.4% of the patients in category 4 developed AMI. Among patients with an abnormal electrocardiogram but with no signs of acute ischemia, the percentage of patients who developed AMI ranged from 38% in category 1 to only 2% in category 4. In patients with signs of acute ischemia on the initial electrocardiogram, the highest percentages of patients who developed AMI were found in category 1: 95% of those with new Q waves and 93% of those with ST elevation. Also, in category 2, the percentages of patients who developed infarction were high in patients with Q waves (82%) and ST elevation (82%), and were 49 and 47%, respectively, in patients with ST depression and T-wave inversion. Twenty percent of the patients in category 3 and 2% of those in category 4 with electrocardiograms showing ischemia developed an infarction.

DISCUSSION

Chest pain or other symptoms suggestive of AMI occur frequently. At our hospital, patients with these symptoms made up 19% of all those presenting to the medical emergency room.[8] The evaluation of these patients is often difficult. The fact that only less than half of the patients admitted to the coronary care units actu-

ally develop AMI[1-7] reflects the present strategy of most hospitals, i.e., to admit any patient with a suspicion of AMI to the coronary care unit. Recently, the possibility of effective early intervention, especially with thrombolytic agents, has further emphasized the importance of the early diagnosis of AMI.

In the emergency room the physician on duty traditionally uses history, clinical status and electrocardiogram to diagnose or exclude AMI. In this study, we looked at the accuracy of this early diagnosis, first when a combination of these variables was used, with the patients being prospectively categorized according to the initial degree of suspicion of AMI, and then when the electrocardiogram was used alone. In our study, 20% of the patients admitted actually developed AMI, and thus many patients without an infarct were hospitalized. This incidence of infarction may seem low; however, we did not study a coronary care unit population, but included in the analysis all patients admitted to a hospital bed. A similar infarction rate has previously been reported.[9]

When we look at the results of our categorization of the patients, we find that categories 1 and 2 together make up 1,705 of the 4,690 patients (36%) admitted from the emergency room, and that 723 of the 921 AMIs (78%) developed in these patients. However, 192 of the AMIs (21%) developed in the 2,519 of all hospitalized patients (53%) belonging to category 3. Thus, 1 of 5 AMIs developed in patients with a vague suspicion of AMI in the emergency room. These data strongly indicate that patients in category 3 should be admitted. However, only 8% of the patients in category 3 developed AMI, and it appears justifiable to observe these patients initially in a regular or intermediate ward for transfer to the coronary care unit when necessary.

In previous studies on the possibility of diagnosing myocardial infarction in the emergency room, it has been shown that the physician's estimate of the probability of infarction is a good predictor of infarction,[5] and different means to help the emergency room physicians have been developed. A predictive model based on 4 clinical variables improved the accuracy of infarct diagnosis when compared with clinical judgment.[10] A computer-derived protocol combined with the physician's clinical judgment improved the accuracy and positive predictive value of the admitting doctor's decision that the patients should be admitted to an intensive care area.[2] A mathematic instrument based on 9 variables increased diagnostic accuracy and reduced the admission rate to the coronary care unit.[11] However, these different diagnostic aids have not come into widespread clinical use.

In our study, 1,109 of the admitted patients (24%) had an ischemic electrocardiogram. Of these patients, 563 (51%) developed AMI, totaling 61% of all AMIs. Most of the admitted patients — 1,964 (42%) — had an abnormal electrocardiogram without acute ischemic signs; 268 (14%) of these patients developed AMI, totaling 29% of all AMIs. Thus, 66% of the admitted patients had abnormal electrocardiograms. Of these patients, 27% developed AMI, totaling 90% of all 921 AMIs. In 2 studies on patients in coronary care units, 64 and 77%[12,13] had abnormal electrocardiograms, and AMI developed in 57 and 41% of these patients, respectively. In 2 studies on patients admitted to the hospital (i.e., not just to the coronary care unit but to general wards as well) because of suspected AMI, 63 and 83% had abnormal electrocardiograms, with rates of AMI of 34 and 63%, respectively.[3,14]

We found ST elevation and new Q waves on the admission electrocardiogram to be the most predictive patterns for AMI, and ST depression and T-wave inversion to be less predictive. These findings are in accordance with previous results.[15]

Of our admitted patients, 1,576 (34%) had a normal initial electrocardiogram. Only 90 (6%) of these patients developed AMI, but that still indicates that 10% of all AMIs developed in patients with a normal electrocardiogram in the emergency room. In other studies, between 12 and 37% of patients admitted for suspected infarction had normal initial electrocardiograms,[3,12,14,16,17] and AMI occurred in 10 to 40% of these patients.[3,12,14,17] Thus, our study showed a lower rate of infarct development, and suggests that it is not necessary to observe patients with normal electrocardiograms in the coronary care unit, unless they have typical symptoms of AMI, severe heart failure or any other reason for coronary care unit treatment.

Table II shows that the percentage of patients developing AMI in relation to the initial electrocardiogram also varies with the clinical suspicion of AMI, expressed as categories 1 to 4. Thus, for patients with normal electrocardiograms, the percentages developing AMI are high in categories 1 and 2, but, as expected, low in categories 3 and 4. Likewise, for patients with abnormal electrocardiograms without acute ischemia and for patients with acute ischemic electrocardiographic patterns, the rate of infarct development is lower the lower the clinical suspicion of AMI.

Few patients were judged to belong to category 1, which probably reflects the difficulty of diagnosing AMI without hospital observation. According to the definition, all 279 patients in category 1 should have ST elevation. However, only 232 (83%) actually had ST elevation, and 4 patients (2%) even had a normal electrocardiogram, which is an example of the discrepancies between the reading of the doctor on duty and the official study reading of the electrocardiogram.

Other methods of early diagnosis of AMI are cardiac enzyme determinations and thallium scintigraphy. Analysis of creatine kinase and creatine kinase-MB in the emergency room has not been shown to be a useful method,[4,18,19] but myoglobin analysis has been demonstrated to give early information on the diagnosis.[20] Myocardial scintigraphy has been proposed as an additional method for evaluation of patients with suspected AMI in the emergency room.[21,22] However, this method cannot be performed in every hospital and, like the enzyme analyses, takes considerable time.

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Usefulness of Severity of Myocardial Ischemia on Exercise Testing in Predicting the Severity of Myocardial Ischemia During Daily Activities

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To determine the relation between myocardial ischemic indexes on exercise testing and on ambulatory Holter recording, 60 patients with stable coronary artery disease who exhibited an ischemic response to both testing procedures were studied. All patients performed a Bruce protocol exercise test and underwent 24-hour Holter recording within 2 weeks without antianginal medications. Mean exercise duration was 7.4 ± 2.8 minutes, mean heart rate at 1-mm ST depression was 118 ± 20 beats/min and mean maximal ST depression during exercise was 2.2 ± 1 mm. During Holter recording the average number of ischemic episodes was 4.7 ± 2.6 per patient, mean duration of daily ischemia was 62 ± 54 minutes, mean maximal ST depression was 3.2 ± 1.3 mm and average heart rate at 1-mm ST depression was 93 ± 17 beats/min. Overall, the correlations between ischemic indexes on both testing procedures were very weak (mean $r^2 = 0.054$). The only exercise variable that had a significant correlation ($p < 0.05$) with all Holter variables was heart rate at 1-mm ST depression, yet it correlated very weakly ($0.064 \leq r^2 \leq 0.125$) with most Holter covariates and had a better correlation ($r^2 = 0.256$) only with average heart rate at 1-mm ST depression during Holter.

Thus, ischemic indexes on exercise testing cannot accurately predict ischemic indexes on ambulatory Holter recording in patients with stable coronary artery disease who exhibit ischemic changes on both tests. These findings indicate that a great portion of the variability of Holter ischemic indexes is dependent on factors other than those represented by exercise testing indexes, and that Holter recording in the ambulatory setting might provide clinically relevant information in addition to that obtained by exercise testing in selected subsets of patients.

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Exercise testing and ambulatory electrocardiographic monitoring are frequently used in detecting and evaluating myocardial ischemia in patients for suspected or proved coronary artery disease.[1–8] Previous studies have indicated that patients with negative or only mildly positive exercise testing responses rarely exhibit spontaneous ischemic episodes during ambulatory electrocardiographic monitoring.[9–11] However, the interrelations between ischemic indexes during exercise testing and ambulatory electrocardiographic monitoring among patients who exhibit ischemic changes on both tests have not been systematically studied. Few previous studies have suggested that the severity of ischemic indexes during exercise testing can predict the severity of ischemic indexes during Holter monitoring.[11–14] However, most of these studies have dealt with nonhomogeneous patient populations with regard to the inclusion of patients with negative results on exercise testing and patients who were treated with various antianginal medications. This study determines whether the severity of ischemia during exercise testing can predict the severity of ischemia during ambulatory Holter monitoring in stable patients who had ischemic changes on both tests.

METHODS

Patients: Sixty patients with known coronary artery disease, positive treadmill stress test and ≥2 ischemic episodes during 24-hour Holter recording were studied. The diagnosis of coronary artery disease was established according to ≥1 of the following 3 criteria: angiographic findings of significant coronary disease (≥70% stenosis in ≥1 major coronary artery) (n = 19), previous myocardial infarction (n = 10), and typical effort-induced angina (n = 42). Of 31 patients with only effort-induced angina, 25 had an exercise-induced

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reversible defect on thallium-201 scintigraphy. There were 53 men and 7 women, aged 32 to 78 years (mean ± standard deviation 59 ± 10.5). All 60 patients performed treadmill exercise testing and underwent 24-hour Holter monitoring within a 2-week period. During that period, all patients were without antianginal medications. All patients gave their informed consent to participate in the study after the study protocol was approved by the institutional committee on human research of our university.

Exercise testing: A Bruce protocol exercise stress test was performed using a Quinton 3000 treadmill. Leads aVF, V_3 and V_5 were continuously monitored, and recorded every minute. Twelve-lead electrocardiogram and blood pressure were recorded every 3 minutes. During the recovery period, blood pressure and 12-lead electrocardiogram were recorded every minute for ≥5 minutes or until ischemic electrocardiographic changes disappeared. Patients were instructed to exercise until the onset of severe chest pain or fatigue. In addition, exercise was stopped if ST depression exceeded 3 mm, systolic blood pressure decreased ≥20 mm Hg or age-adjusted maximal predicted heart rate was achieved. The exercise test result was regarded as positive for ischemia if ≥1 mm of horizontal or downsloping ST depression, measured 80 ms after the J point, was observed in ≥2 electrocardiographic leads.

The following exercise parameters were recorded in each patient: total duration, heart rate at 1-mm ST depression, maximal heart rate during exercise, maximal ST depression in any electrocardiographic lead, and presence or absence of typical chest pain.

Ambulatory electrocardiographic monitoring: All patients underwent ambulatory 24-hour electrocardiographic recording by ACS reel-to-reel 2-channel AM recorders calibrated to 10 mm/1 mV. Recorders were equipped with an "event button" that the patient was instructed to activate when any chest pain or discomfort was experienced. Ag-AgCl skin electrodes were attached to a well-shaved and scrubbed chest wall. The exploring electrodes were attached to the V_3- and V_5-like positions.[15] The CardioData Prodigy System, combined with a PDP 11/73 computer, was used for the digitization and analysis of the Holter tapes. Holter data were analyzed by a highly experienced technician, using a validated computer algorithm (version 7.07) for ST analysis.[16] The ST analysis was performed in both channels in a semiautomatic-interactive method. The technician had to set the isoelectric level at the PR segment and the J point. The system determined the ST slope by measuring the average level of the ST segment 60 ms after the J point in consecutive 30-second samples. Any ST deviation (elevation or depression) from the isoelectric level, and its type (upsloping or downsloping), was displayed on the ST trend. The ST changes during the entire monitoring period were plotted in 2-channel ST-trend histograms. A heart-rate trend was plotted on the same time scale as the ST trend in order to enable accurate determination of the heart rate at the onset of ischemic episodes. Electrocardiographic samples were printed out in real time, 2 minutes before the onset of ST depression, at the onset of ischemia (1 mm of ST depression), at maximal ST depression, at maximal heart rate and on return to the isoelectric line. Each episode was visually verified by a physician, both from the ST trend and from the real-time printouts. An ischemic episode was defined as a transient depression of the ST segment ≥1 mm, horizontal or downsloping, that lasted for ≥1 minute and after which a return to baseline was observed.

TABLE I Exercise Testing Results in 60 Patients

Exercise Parameter	Range	Mean ± SD
Duration (min)	3.5–13.5	7.4 ± 2.8
Heart rate at 1-mm ST depression (beats/min)	70–170	118 ± 20
Maximal heart rate (beats/min)	86–182	143 ± 21
Maximal ST depression (mm)	1–5	2.2 ± 0.99
Anginal pain (pts.)	26	—

SD = standard deviation.

The following Holter parameters (per patient) were recorded: number of ischemic episodes, total duration of ischemia, maximal ST depression observed in any channel, and minimal, maximal and mean heart rate at 1-mm ST depression.

Statistical analysis: The 2 testing procedure results were compared using the Pearson product-moment correlation coefficient. To account for outliers influence and the nonparametric distribution of some variables, all correlations were redetermined after logarithmic transformation of the variables. Selected continuous variables were dichotomized at their median value and compared using the chi-square test. A 2-tailed p value <0.05 was considered statistically significant. Each Holter variable was linearly regressed on a combination of 3 selected exercise variables in order to determine the dependency of the variability of Holter ischemic indexes on that of exercise ischemic indexes.

RESULTS

Exercise testing results (Table I): Exercise duration ranged from 3.5 to 13.5 minutes (mean 7.4), heart rate at onset of ischemia ranged from 70 to 170 beats/min (mean 118) and maximal ST depression ranged from 1 to 5 mm (mean 2.2). Ischemia was accompanied by chest pain in 26 of 60 patients (36.7%).

Holter monitoring results (Table II): During 1,440 hours of Holter monitoring in 60 patients, 283 ischemic

TABLE II 24-Hour Holter Monitoring Results in 60 Patients

Holter Parameter	Range	Mean ± SD
No. of ischemic episodes	2–11	4.7 ± 2.6
Total ischemic period (min)	5–242	62 ± 54
Maximal ST depression (mm)	1–8.2	3.2 ± 1.3
Heart rate at 1-mm ST depression (beats/min)		
Mean	74–144	103 ± 16
Minimal	60–140	93 ± 17.3
Maximal	83–151	112 ± 16
Silent episodes (%)	0–100	75 ± 30

SD = standard deviation.

episodes were detected. The number of episodes per patient ranged from 2 to 11 (mean 4.7) and the total duration of ischemia ranged from 5 to 242 minutes (mean 62). The mean heart rate at 1-mm ST depression ranged from 60 to 140 beats/min (mean 93) and the maximal ST depression ranged from 1 to 8.2 mm (mean 3.2). Of the 283 ischemic episodes, 75.3% were silent and 24.7% were symptomatic.

Correlation between ischemic indexes on exercise testing and on Holter monitoring: Three selected scatter diagrams relating exercise ischemic indexes to Holter ischemic indexes are presented in Figures 1 to 3. None of the scatter diagrams visually suggested a nonlinear relation between covariate pairs before or after logarithmic transformation. The cross correlation matrix of 3 exercise testing and 6 Holter-monitoring ischemic indexes is presented in Table III. Most of the ischemic indexes during Holter were very weakly correlated to the ischemic indexes during exercise (similar correlations were obtained for all covariate pairs after logarithmic transformation). The number of ischemic episodes during Holter had a significant but weak correlation ($p < 0.01$, $r = -0.354$) with the heart rate at 1-mm ST depression during exercise, and was independent of exercise duration ($r = -0.178$) and of maximal ST depression during exercise ($r = 0.094$). The total ischemic period during Holter had a significant but weak correlation only with the heart rate at 1-mm ST depression during exercise ($p < 0.05$, $r = -0.253$), and maximal ST depression during Holter correlated significantly but weakly only with the heart rate at 1-mm ST depression during exercise ($r = -0.273$). The minimal, maximal and mean heart rates at 1-mm ST depression during Holter were all significantly and more strongly correlated to the heart rate at 1-mm ST depression during exercise ($p < 0.01$, $0.430 \leq r \leq 0.506$) than other Holter variables. All the covariates in Table III were dichotomized at their median value and a chi-square test was performed for the number of patients corresponding to the dichotomies of each covariate pair. This test yielded a nonsignificant 2-tailed p value (>0.05) for all the aforementioned ischemic indexes[1] pairs, except for heart rate at 1-mm ST depression during exercise (dichotomized at 120 beats/min) and mean heart rate at 1-mm ST depression during Holter (dichotomized at 100 beats/min [$p < 0.005$, odds ratio = 5.25]).

Linear regressions of each Holter variable on 3 selected exercise variables (exercise duration, heart rate at 1-mm ST depression and maximal ST depression) revealed that the linear combination of exercise ischemic indexes correlated poorly with most ischemic indexes on Holter, except for the mean, minimal and maximal heart rate at 1-mm ST depression ($p < 0.01$ for all 3 Holter covariates, $0.217 \leq r^2 \leq 0.271$).

DISCUSSION

The principal findings of this study indicate that most ischemic indexes during exercise testing cannot

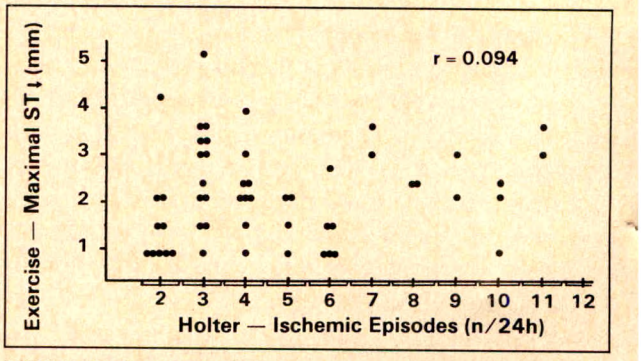


FIGURE 2. Correlation between maximal ST depression (↓) during exercise test and number of ischemic episodes during 24-hour Holter recording.

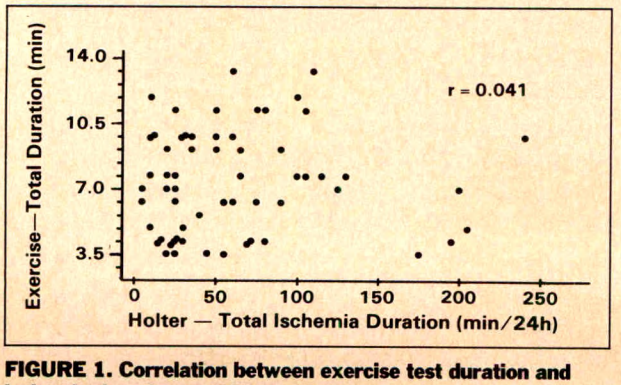


FIGURE 1. Correlation between exercise test duration and ischemia duration on 24-hour Holter recording.

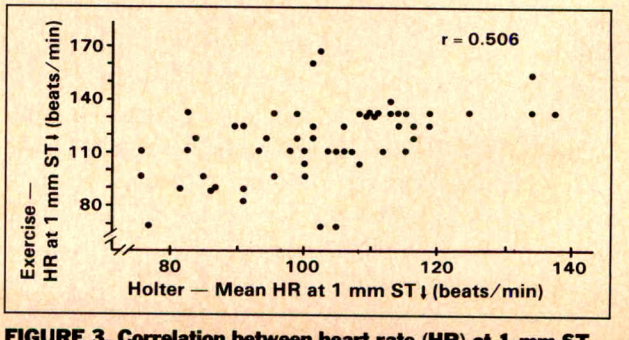


FIGURE 3. Correlation between heart rate (HR) at 1-mm ST depression (↓) during exercise testing and during 24-hour Holter recording.

TABLE III Correlation Between Exercise and Holter Ischemic Indexes

Holter Monitoring	Exercise Testing		
	Total Duration	Maximal ST Depression	Heart Rate at 1-mm ST Depression
No. of episodes	−0.178	0.094	−0.354*
Total ischemic period	0.041	0.111	−0.253†
Maximal ST depression	0.010	0.112	−0.273†
Heart rate at 1-mm ST depression			
Minimal	0.170	−0.208	0.494‡
Maximal	0.266†	−0.175	0.430*
Mean	0.241	−0.183	0.506‡

*p = 0.01; †p <0.05; ‡p <0.001.
Values in table correspond to the Pearson product moment correlation coefficient between covariate pairs.

accurately predict ischemic indexes during Holter monitoring in patients with stable coronary artery disease who exhibit ischemic changes on both tests. The ischemic threshold (heart rate at 1-mm ST depression) during exercise was the only exercise covariate that had significant correlations with all ischemic indexes on Holter. However, its correlations with the number of ischemic episodes and the total ischemic period during Holter, which are the 2 Holter covariates most often used to quantify the "total ischemic burden" in the ambulatory setting, were quite weak (r^2 <13%), whereas its correlation with the average ischemic threshold during Holter was of medium strength (r^2 = 26.5%) and therefore physiologically meaningful. These findings indicate that a great portion of the variability in Holter ischemic indexes is dependent on factors other than those represented by exercise testing ischemic indexes. The significant and meaningful correlation between the ischemic thresholds during both testing procedures points to a common mechanism that operates in both exercise-induced and ambulatory ischemia. This mechanism (increase in myocardial oxygen demand in the presence of fixed coronary stenoses) is probably greatly modified in the ambulatory setting by factors such as the dynamic changes in the autonomic neural cardiac control[17] and other factors that have not been well defined.

Comparison with previous studies: Most previous studies that have examined the relations between ischemic indexes during exercise testing and ambulatory Holter monitoring have included in their analysis patients with known coronary artery disease and positive exercise testing; however, only 37 to 60% of the patients also had ischemic ST-segment changes on ambulatory Holter recording.[10–14] These studies have concluded that ambulatory ischemia is rarely detected among patients with negative stress test results or among patients in whom exercise testing is positive for ischemia only at high work loads. However, the reported relations between ischemic indexes during exercise and Holter monitoring in these studies are based on analyses not exclusively directed at the subset of patients with coronary artery disease who exhibit ischemic changes on both tests. Some previous studies have reported a significant relation between the number of ischemic episodes during Holter monitoring and the time to 1-mm ST depression during exercise,[11–13] whereas the total duration of ambulatory ischemia was found to be significantly related to exercise testing covariates only by Quyyumi et al[11] and not by Mody et al.[10]

Because of several reports that have suggested that ambulatory ischemia carries an independent risk for subsequent cardiac events,[10,14,18,19] the objective of this study, namely to determine the relations between quantitative measures of ambulatory and exercise-induced ischemia among patients who exhibit both, seems relevant and might answer practical questions such as: Should a patient with a positive stress test at a medium or a low work load undergo ambulatory Holter recording as a part of his evaluation?

Study limitations: We did not use some exercise testing covariates that were used by previous investigators. However, because most exercise covariates have high correlations among themselves, we assume that our selection bias in this regard is negligible. Furthermore, we included a Holter covariate that has not been used by most previous studies, namely the average heart rate at 1-mm ST depression, and indeed this variable was the only one that had a meaningful relation with one of the exercise covariates. Our study does not include clinical follow-up data, and therefore, our conclusions with regard to the clinical implications of the results should be interpreted with caution until future studies on the prognostic value of ambulatory ischemia indexes in a similar subset of patients are performed.

Exercise testing was performed in this study using the Bruce protocol. It has recently been suggested that the relations between ischemic indexes obtained by exercise testing and those obtained by ambulatory monitoring might be dependent on the exercise protocol used. This might suggest that the conclusions of the present study should be confined only to patients under-

going the Bruce protocol exercise test. However, Redwood et al[20] examined the ischemic threshold during bicycle exercise testing and compared the triple product at 1-mm ST depression during a standard protocol with that observed during a more gradual protocol in 12 patients with stable angina pectoris and angiographically proved coronary artery disease. The ischemic threshold during both exercise protocols was similar. Our own experience in comparing the Bruce to the Naughton treadmill exercise protocols in 20 patients with stable angina pectoris (unpublished data) revealed a nonsignificant difference in the rate pressure product at 1-mm ST depression between the 2 protocols (18,700 vs 17,909, respectively).

Clinical implications: Because the present study has revealed an overall weak correlation between ischemic indexes on both tests, performance of ambulatory Holter recording in selected patients with an ischemic response at low work loads during stress testing might convey clinically relevant information in addition to that obtained by exercise testing.

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Systemic Neurohumoral Activation and Vasoconstriction During Pacing-Induced Acute Myocardial Ischemia in Patients with Stable Angina Pectoris

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To identify the effect of myocardial ischemia on systemic neurohormones and vascular resistance, 32 untreated, normotensive patients with coronary artery disease underwent incremental atrial pacing until angina. Arterial and coronary venous lactate and arterial values of catecholamines and angiotensin II were determined at control, at maximal pacing rates, and at 1, 2, 5 and 30 minutes after pacing. Based on pacing-induced ST-segment depression (≥0.1 mV) or myocardial lactate production, or both, patients were selected as ischemic (n = 25) or nonischemic (n = 7). Baseline clinical and hemodynamic data were comparable. During pacing, chest pain was similar (20 ischemic vs 7 nonischemic patients). Also, hemodynamic measurements were comparable, except for contractility, which did not improve, and left ventricular end-diastolic pressure, which significantly increased in ischemic patients. Moreover, during ischemia arterial pressures increased significantly (13%) and systemic resistance increased from 1,470 ± 60 (control) to 1,632 ± 76 dynes · s · cm^{-5} 5 minutes after pacing ($p < 0.05$) in ischemic but not in nonischemic patients. Pacing did not affect neurohormones in nonischemic patients. In contrast, norepinephrine in ischemic patients increased significantly from 1.7 ± 0.2 (control) to 2.6 ± 0.3 (maximal pacing) and to 3.0 ± 0.4 nmol/liter (1 minute after pacing), whereas angiotensin II levels increased from 6.2 ± 1.4 (control) to 9.3 ± 2.1 pmol/liter (1 minute after pacing, $p < 0.05$). Epinephrine only increased during maximal rates (0.9 ± 0.1 vs 0.6 ± 0.1 nmol/liter at control, $p < 0.05$). Thus, myocardial ischemia activates circulating catecholamines and angiotensin II, accompanied by systemic vasoconstriction. Because the latter may amplify ischemia, modulation of this neuroendocrine stimulation may be of therapeutic value.

(Am J Cardiol 1991;68:181–186)

In humans, systemic catecholamines and circulating renin-angiotensin levels become activated during acute myocardial infarction, depending on the degree of cardiac dysfunction.[1–6] Whether myocardial ischemia also results in neuroendocrine activation as a result of an acute, ischemia-induced reduction in cardiac pump function, is less well defined. In humans, available data do not uniformly indicate significant changes in plasma or urinary catecholamines during exercise- or pacing-induced ischemia.[2,7–11] Whereas an early study suggested increased catecholamine levels during exercise-induced angina,[2] this could not be confirmed in a more recent investigation in which more sensitive and specific biochemical techniques were applied.[7] Besides these conflicting reports, it is unknown whether myocardial ischemia affects the circulating renin-angiotensin system. Furthermore, no data exist on the hemodynamic consequences of ischemia-induced systemic neurohumoral activation in humans. The present study investigates sequential changes in systemic neurohormones and hemodynamics during pacing-induced ischemia in normotensive patients with coronary artery disease and in similar patients who did not develop ischemia during the test.

METHODS

Patient: After the protocol was approved by the institutional ethical review board and informed consent obtained, 32 patients (29 men and 3 women, average age 57 years [range 37 to 69]) were studied. Subjects were referred for coronary angiography for the evaluation of angina-like chest pain. Objective signs of ischemia or a previous myocardial infarction were not obligatory for inclusion, but patients had to be normo-

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tensive without symptoms of heart failure. Exclusion criteria included previous myocardial infarctions <1 month old, unstable angina, valvular heart disease, conduction disturbances or the use of diuretic drugs. Cardiac therapy was withheld 36 to 72 hours before the study. Only short-acting nitroglycerin was allowed until 6 hours before the investigation. Significant coronary artery disease, defined as ≥70% diameter narrowing, was present in 28 patients. Of these, 10 had 1 artery, 11 had 2 arteries and 7 had 3 arteries so narrowed. Objective signs of ischemia during ergometry testing before the study (≥0.1 mV ST-segment depression) were present in 22 patients, whereas ≥1 documented myocardial infarctions were present in 18.

Catheterization procedures: Patients were studied at the same time in the morning after an overnight fast without premedication. After coronary angiography, using the Seldinger technique, an 8Fr Sentron pigtail microtip manometer catheter was advanced into the left ventricle through a 9Fr arterial Desilet introducer system in a femoral artery. The side arm of this system was used to measure arterial pressures. A 7Fr triple-lumen thermodilution catheter was positioned with its tip in a pulmonary artery. Finally, a 7Fr Zucker bipolar pacing catheter or 7Fr thermodilution pacing catheter was advanced into the midportion of the coronary sinus, so that the tip of the catheter was ≥3 cm beyond the orifice of the coronary sinus; thus, its position was stable and rapid blood sampling was ensured. The position of the catheters was subsequently recorded on video disc and frequently checked during the study.

Measurements and calculations: Fluid-filled catheters were calibrated, using Bentley transducers with a zero reference level set at midchest. The micromanometer pressure was balanced to zero and superimposed on the conventional pressure recording. All pressures, the first derivative of left ventricular pressure and the thermodilution-derived cardiac output signal were recorded on paper at different paper speeds, using a CGR 1000 cathlab system. Pressures and pressure-derived contractility indexes were measured on-line from 12 to 15 successive beats, using a Mennen Medical catheterization laboratory computer system. Likewise, cardiac output measurements were determined on-line. At the end of the study, the femoral arterial pressure curves were compared with simultaneous recordings from the ascending aorta by the Sentron catheter.

Hemodynamic variables: Measured variables included left ventricular peak systolic and mean and end-diastolic pressures (mm Hg), pressure-derived contractility indexes (the first derivative left ventricular pressure [mm Hg/s] and Vmax (s^{-1}), mean and phasic systemic and pulmonary arterial pressures (mm Hg), mean right atrial pressure (mm Hg) and cardiac output (liters/min). From these, systemic vascular resistance (dynes · s · cm^{-5}), stroke index (ml/beat/m^2) and stroke work index (g/m/m^2) were calculated.[12]

Electrocardiographic parameters: Leads I, II and V_5 were monitored continuously to measure heart rate. ST segments were determined at a paper speed of 100 mm/s in 3 successive beats, 60 ms after the J point of the QRS complex, using a calibrated magnifying lens.

Metabolic and neurohumoral parameters: Coronary venous and arterial lactate levels were assessed as reported previously.[13] For the determination of catecholamines, 3 ml of blood were collected from the left ventricle in ice-cold syringes and transferred into precooled tubes containing 500 IU of heparin and 3 mg/ml of glutathion. In a similar fashion, 3 ml of blood were transferred into precooled tubes containing 4 mg of ethylene diaminetetraacetic acid and 0.06 mg of O-fenantroline for angiotensin II assay. Samples were immediately centrifuged under cooled conditions at 3,000 revolutions every 10 minutes and frozen at −20°C. Norepinephrine, epinephrine and dopamine were determined by radioenzymatic assay using high-pressure liquid chromatography to separate the radioactive products.[14] Angiotensin II was assessed by radioimmunoassay.[15]

Study protocol: Repeated control measurements of all variables were performed at approximately the same time in the morning, 1.5 to 2 hours after entering the laboratory, and 20 and 40 minutes after instrumentation and coronary angiography, respectively. Next, the pacing stress test was performed with increments in heart rate of 10 beats every 2 minutes until significant angina-like pain, atrioventricular block or a maximal rate of 170 beats/min were reached. Significant angina-like pain was defined as the level of pain at which the patient typically would rest or take nitroglycerin. All variables were redetermined at maximal rates, just before cessation of pacing, followed by measurements at 1, 2, 5 and 30 minutes after pacing. Left ventricular end-diastolic pressure and lactate were also measured at 10 and 15 seconds after pacing, respectively. Cardiac output was determined at control and 3 to 5 minutes after pacing.

Statistical analysis: Changes from baseline values were calculated for neurohormones and hemodynamic variables in each patient. Statistical differences were assessed using a paired *t* test with a p value <0.05 considered significant (2-sided). Baseline values for hemodynamic variables and changes from control during pacing in patients who became ischemic during the test were compared with those who did not using an unpaired Student test with a p value <0.05 to detect significant differences. Values are given as averages (×) and standard errors of the mean.

RESULTS

Control period: At baseline, none of the patients had clinical signs of ischemia. Values for norepinephrine and epinephrine ranged between 0.7 and 3.15 nmol/liter and between 0.17 and 1.55 nmol/liter, respectively. Angiotensin II varied from <2 (in 2 patients) to 24 pmol/liter.

Pacing period: Based on objective signs of ischemia during pacing, i.e., ST-segment depression of ≥0.1 mV or myocardial lactate production, or both, patients were classified as ischemic (n = 25) or nonischemic (n = 7). Of these, 20 ischemic and 5 nonischemic patients had chest pain during pacing. Groups were comparable as to sex, age, number of previous infarcts and left ventricular volumes and ejection fraction (Table I). In contrast, objective signs of ischemia during prestudy exercise tests and significant coronary lesions were more prominent in ischemic patients.

Sequential hemodynamic changes during and after pacing: Baseline hemodynamic variables were similar in both groups (Table II). Also, during pacing, maximal changes in heart rate, left ventricular systolic pressure and the double product were comparable, as well as pacing-induced alterations in coronary sinus flow, coronary resistance and myocardial oxygen extraction and consumption. In contrast, contractility indexes (e.g., Vmax) did not change during pacing in ischemic patients, compared with a significant 27% improvement in nonischemic subjects. Also, left ventricular pressure, at 10 seconds postpacing, was significantly elevated in ischemic but not in nonischemic patients. Arterial pressures increased by 13% in ischemic patients during maximal pacing, whereas systemic resistance was still elevated at 5 minutes after pacing (1,632 ± 76 vs 1,470 ± 60 dynes · s · cm^{-5} [control], $p < 0.05$, Figure 1]). No such changes occurred in nonischemic patients.

Sequential electrocardiographic and metabolic changes during pacing: By design, significant repolarization disturbances only occurred in ischemic patients, persisting until 2 minutes after pacing (Figure 2). Pacing did not affect myocardial lactate metabolism in those without ischemia. In contrast, in ischemic patients, myocardial lactate extraction, present at control, changed to production during maximal pacing and persisted for 2 minutes after pacing (maximal value −71 ± 16% at 15 seconds after pacing [Figure 2]).

TABLE I Baseline Clinical and Angiographic Characteristics of Ischemic and Nonischemic Patients

	Ischemic (n = 25)	Nonischemic (n = 7)
Sex	24 M/1 F	5 M/2 F
Age (years)	55 ± 1.8	65 ± 1.2
Positive ECG	19	3
Previous infarct	15	3
No. of coronary arteries narrowed >70% in diameter by angiogram		
0	0	4
1 (LCA)	7	3
2	11	0
3	7	0
Left ventricular ejection fraction (%)	53 ± 3	51 ± 6
Left ventricular end-diastolic volume (ml/m^2)	63 ± 4	69 ± 9

ECG = electrocardiogram; LCA = left coronary artery.

Effect of pacing-induced ischemia on systemic neurohormones: Pacing did not affect arterial catecholamines or angiotensin II levels in nonischemic subjects (Table III). In contrast, significant neurohumoral changes were observed during myocardial ischemia. In patients with ischemia, arterial norepinephrine increased significantly during pacing, with maximal changes (76%) at 1 minute after pacing. Concomitantly, arterial angiotensin II levels increased significantly by 39% (Figure 3). By contrast, epinephrine levels only increased during pacing. Norepinephrine and angiotensin II levels returned to baseline values between 2 and 5 minutes after pacing. Dopamine levels did not change.

DISCUSSION

Systemic neurohumoral activation frequently accompanies acute myocardial infarction, particularly when complicated by cardiac pump failure.[1–6] Like-

TABLE II Hemodynamic Variables at Control and Maximal Pacing Rates in Ischemic Versus Nonischemic Patients

Group	HR (beats/min)	LVSP (mm Hg)	LVEDP (mm Hg)	MAP (mm Hg)	Vmax (s^{-1})	CBF (ml/min)	DP (beats/min · mm Hg 10^{-3})
Ischemic							
Control	85 ± 3.5	148 ± 6	14 ± 1.5	112 ± 4	53 ± 3	109 ± 8	12.2 ± 8.6
Maximal pacing	152 ± 4	143 ± 7	15 ± 2*	127 ± 4†	57 ± 3	193 ± 15	21.5 ± 1.1
10 seconds p-p			25 ± 3*				
Nonischemic							
Control	81 ± 4	142 ± 6	12 ± 1	110 ± 6.5	56 ± 5	122 ± 14	11.5 ± 0.6
Maximal pacing	147 ± 7	140 ± 9	7 ± 1	115 ± 8	71 ± 7†	186 ± 31	20.7 ± 1.8
10 seconds p-p			13 ± 1				

*$p < 0.05$ ischemic group versus nonischemic group; †$p < 0.05$ Δ control-maximal pacing, ischemic group versus nonischemic group
CBF = coronary venous blood flow; DP = double product; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; MAP = mean arterial pressure; p-p = after pacing.

TABLE III Effect of Pacing on Arterial Neurohormones in Ischemic Versus Nonischemic Patients

	C	MAX	1′ P-P	2′ P-P	5′ P-P	30′ P-P
Norepinephrine (nmol/liter)						
I group	1.7 ± 0.2	2.6 ± 0.3*	3.0 ± 0.4*	2.4 ± 0.3	2.4 ± 0.3	2.1 ± 0.2
NI group	2.0 ± 0.4	2.3 ± 0.3	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.4	2.0 ± 0.6
Epinephrine (nmol/liter)						
I group	0.60 ± 0.09	0.93 ± 0.13*	0.71 ± 0.10	0.67 ± 0.09	0.70 ± 0.13	0.63 ± 0.08
NI group	0.54 ± 0.09	0.62 ± 0.10	0.57 ± 0.13	0.61 ± 0.13	0.58 ± 0.14	0.66 ± 0.19
Dopamine (nmol/liter)						
I group	0.50 ± 0.07	0.54 ± 0.08	0.49 ± 0.09	0.35 ± 0.07	0.43 ± 0.12	0.53 ± 0.05
NI group	0.35 ± 0.08	0.33 ± 0.08	0.21 ± 0.07	0.24 ± 0.08	0.36 ± 0.08	0.40 ± 0.08
Angiotensin II (pmol/liter)						
I group	6.2 ± 1.4	8.6 ± 2.0*	9.3 ± 2.1*	5.5 ± 0.9	6.0 ± 0.9	6.9 ± 1.8
NI group	5.0 ± 1.5	4.9 ± 1.4	4.7 ± 1.4	4.3 ± 1.4	4.4 ± 1.3	5.8 ± 1.6

*$p < 0.05$ vs control.
C = control; I = ischemic; MAX = maximal pacing rates; NI = nonischemic; P-P = after pacing; ′ = minute(s).

wise, in animal models, long-lasting, severe myocardial ischemia also increases neuroendocrine activation.[16] In contrast, whether short periods of moderate ischemia in humans may equally affect peripheral neurohumoral systems is not entirely clear. Thus far, data on catecholamine stimulation during exercise- or pacing-induced ischemia have been conflicting.[2,7–11,17] Furthermore, no information exists on other neurohormones in this context. The present study clearly demonstrates that myocardial ischemia, induced by atrial pacing in the resting patient with coronary artery disease, results in a significant activation of systemic catecholamines and of the circulating renin-angiotensin system, together with a significant increase in systemic vascular resistance and arterial pressures. Because it may be anticipated that afterload subsequently increases, imposing an extra burden on the already ischemic myocardium, this systemic neurohumoral activation may be of clinical relevance.

The effect of pacing-induced stress and anginal pain on circulating neurohormones: Pacing, per se, does not significantly affect neurohormones. In the present study, nonischemic patients were paced to the same level as the ischemic patients, with similar increases in myocardial oxygen demand and consumption. Nevertheless, arterial neurohumoral levels did not change significantly, despite the fact that 5 nonischemic patients (72%) had chest pain during pacing. The latter indicates that angina is not a prerequisite for neurohumoral activation. Unfortunately, this cannot be proved in our study, because only few ischemic patients were asymptomatic. However, other studies, performed during pacing-induced stress, also did not observe significant changes in systemic catecholamines.[8,10,11] Because of the elusive link between transient myocardial ischemia and angina,[18] neurohumoral activation probably

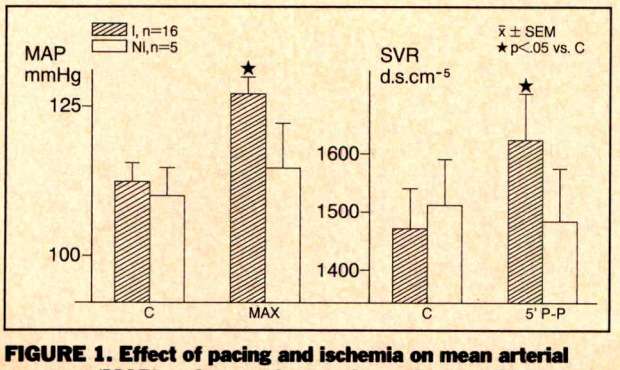


FIGURE 1. Effect of pacing and ischemia on mean arterial pressure (MAP) and systemic vascular resistance (SVR). Both MAP and SVR increased significantly in patients who became ischemic during pacing (I), but not in nonischemic patients (NI). C = control; MAX = maximal pacing rates; p-p = after pacing; SEM = standard error of the mean; ′ = minute.

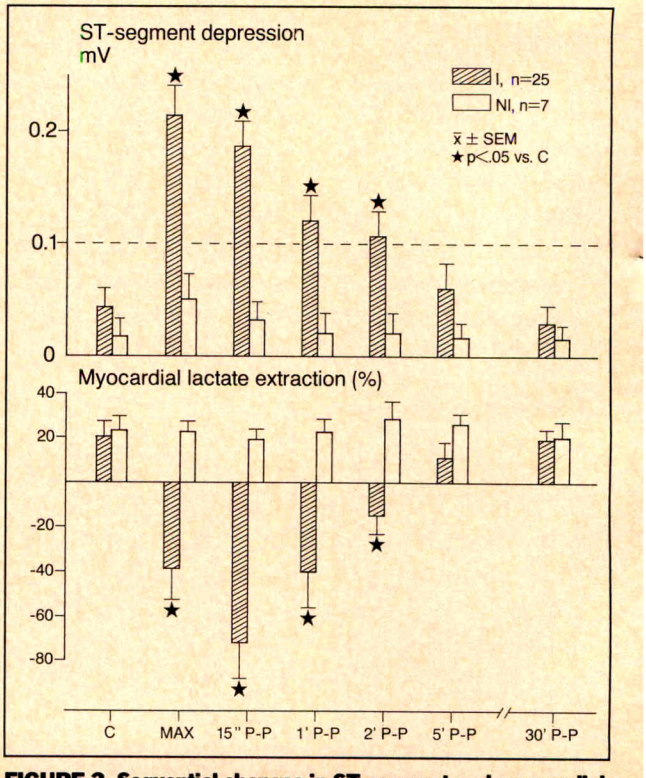


FIGURE 2. Sequential changes in ST-segment and myocardial lactate extraction in ischemic patients (I) persisting until 2 minutes (′) after pacing (p-p), but not in nonischemic patients (NI). C = control; MAX = maximal pacing rates; SEM = standard error of the mean; " = seconds.

does not depend on the occurrence of anginal pain, but rather on presence and degree of myocardial ischemia. Only few ischemic patients in our study did not produce lactate, which suggests predominant anterior wall ischemia. Besides stimulation of mechanoreceptors in this area by hemodynamic or metabolic stimuli and subsequent excitation of the vasomotor center in the medulla oblongata,[18,19] a more pronounced reduction in cardiac pump function could also explain the neuroendocrine activation in this study.

Comparison with other studies of pacing- or exercise-induced ischemia: The inconsistency in observations on catecholamine activation in available patient studies may be explained by different degrees of ischemia. Alternatively, they may be explained by differences in sensitivity and specificity of the biochemical, analytic techniques available at the time of study. Nevertheless, several relatively recent investigations, all performed in a similar model of pacing-induced stress, have been equally inconsistent in their observations on neuroendocrine activation during ischemia.[8,10,17] Because study protocol, type of patients and catecholamine assay techniques were basically comparable, the variability in study results is difficult to explain. Our study differs from these investigations in 2 aspects. First, the objective in the present study was to analyze neurohumoral alterations during ischemia, per se, irrespective of angina, but confirmed by objective signs of ischemia. Only Schwartz et al[8] stipulated the presence of objective evidence for ischemia in their anginal patients. Second, the combined radioenzymatic assay and high-pressure liquid chromatography technique may significantly improve the detection of small changes in catecholamine levels. Moreover, our study differs from previous investigations, since it also investigates alterations in other neurohormones and concomitant hemodynamic changes during ischemia.

Effect of pacing-induced ischemia on circulating angiotensin II levels: In the present study, arterial angiotensin II levels increased significantly during pacing-induced ischemia, but not during equivalent increments in heart rate in nonischemic patients. Thus far, no data are available on the effect of ischemia on the circulating renin-angiotensin system. However, recent animal studies indicate that this system may indeed be influenced by myocardial ischemia.[20,21] Ertl et al[20] demonstrated a significant increase in arterial renin and, to a lesser extent, arterial angiotensin II after 10 minutes of coronary occlusion in a canine model. Also, in their studies a 30-second occlusion of the left anterior descending artery resulted in significant elevations of plasma renin and angiotensin II, whereas fast atrial pacing in the presence of a coronary artery stenosis induced a 50% increment in arterial renin.[20,22] This activation of the circulating renin-angiotensin system by ischemia was not modulated by β-adrenergic blockade, but prevented by nephrectomy. Thus, it may be initiated by renin release from the kidney as a result of renal underperfusion, secondary to ischemia-induced left ventricular dysfunction, which suggests that stimulation of the circulating renin-angiotensin system depends on the severity of myocardial ischemia.

Ischemia-induced neurohumoral activation may result in systemic vasoconstriction: A significant increase in systemic vascular resistance and an increase in arterial pressures was observed in ischemic, but not in nonischemic, patients. Because ischemia-induced cardiac dysfunction and the subsequent decrease in cardiac output primarily will result in a reduction of arterial pressures, secondary counterregulatory forces must supervene. Whether the increase in systemic catecholamines or activation of the circulating renin-angiotensin sys-

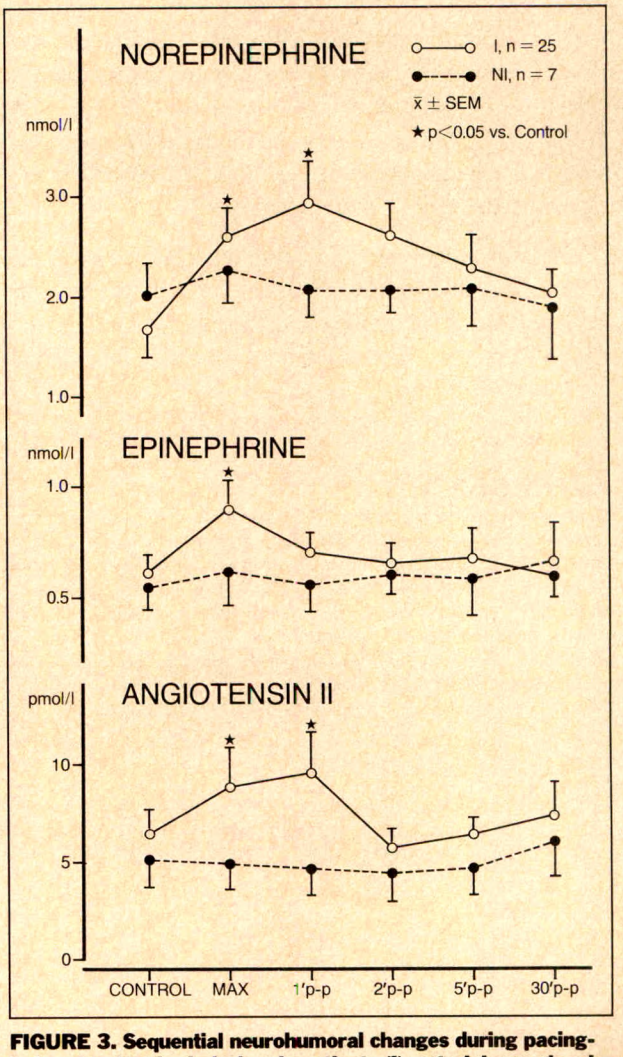


FIGURE 3. Sequential neurohumoral changes during pacing-induced ischemia. In ischemic patients (I), arterial norepinephrine and angiotensin II increased significantly from control to maximal pacing rates (MAX) and at 1 minute (′) after pacing (p-p), whereas arterial epinephrine was elevated at maximal pacing rates. In contrast, in nonischemic patients (NI), pacing does not affect arterial neurohumoral levels. SEM = standard error of the mean.

tem, or both, is causally involved cannot be determined from our studies because specific antagonists of these neurohumoral systems were not administered. Thus, the concomitant change in systemic resistance and neurohormones only suggests such an interrelation, but could be coincidental.

Clinical implications: Our observations were made in the resting, supine patient and do not necessarily apply to the model of exercise-induced ischemia. Exercise by itself results in increased circulating neurohormones, irrespective of the presence or absence of cardiac disorders.[23] In contrast, in the resting patient, with stable and low baseline neurohumoral levels, subsequent activation during ischemia may be clinically significant. Thus, in patients with ischemia at rest, e.g., unstable angina or the early phase of myocardial infarction, a similar or even more pronounced neuroendocrine activation than that in our study may be present with systemic, and possibly coronary, vasoconstriction amplifying the ischemic process. Although their interrelation is still speculative, interventions aimed at modulating neurohumorally induced vasoconstriction, i.e., α-adrenergic antagonists or inhibitors of the renin-angiotensin system, may be useful as (additional) antiischemic therapy in these situations.

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Frequency of Low Serum High-Density Lipoprotein Cholesterol Levels in Hospitalized Patients with "Desirable" Total Cholesterol Levels

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Because the National Cholesterol Education Program guidelines suggest that levels of total serum cholesterol <5.17 mmol/liter (200 mg/dl) are "desirable," we performed a retrospective observational analysis to determine the prevalence of coronary artery disease (CAD) in patients with total cholesterol <5.17 mmol/liter (200 mg/dl) and the prevalence of total cholesterol <5.17 mmol/liter (200 mg/dl) in patients with CAD by angiography. Cholesterol levels <5.17 mmol/liter (200 mg/dl) were found in 1,084 of 2,535 patients (42%) having cholesterol measured on hospital admission; 690 of these 1,084 (64%) had CAD. These patients were mostly men, had a family history of premature CAD, and 60% (414 of 690) had high-density lipoprotein (HDL) cholesterol <0.90 mmol/liter (35 mg/dl). In a separate group of patients defined from the same admission population but having angiographically established CAD, 32% (424 of 1,197) had a total cholesterol <5.17 mmol/liter (200 mg/dl), 59% of whom (252 of 424) had HDL <0.90 mmol/liter (35 mg/dl). An analysis of persons admitted electively for angiography (to exclude any effects of hospitalization per se on serum lipids) revealed a similar proportion of persons with total cholesterol <5.17 mmol/liter (200 mg/dl) (35%), CAD (82%), and HDL <0.90 mmol/liter (35 mg/dl). Our observations suggest that low serum cholesterol levels (<5.17 mmol/liter [200 mg/dl]) are seen frequently in patients suspected of having or who have established CAD; moreover, a false sense of security may be established among physician and patient with the finding of a serum cholesterol level <5.17 mmol/liter (200 mg/dl) — men with a family history of premature CAD and low levels of HDL characterize persons with CAD in this low cholesterol group.

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To facilitate the interpretation of studies implicating cholesterol in the development of coronary artery disease (CAD), the National Cholesterol Education Program recently defined a total serum cholesterol >6.21 mmol/liter (240 mg/dl) as "high," from 5.17 mmol/liter (200 mg/dl) to 6.20 mmol/liter (239 mg/dl) as "borderline," and <5.17 mmol/liter (200 mg/dl) as "desirable."[1] Accordingly, these guidelines suggest that the latter group with desirable total cholesterol levels need no further lipid analysis regardless of the presence of other risk factors for CAD, or CAD itself. Although little data are available on whether the risk profile of this group specifically warrants measurement of lipid parameters other than cholesterol (e.g., triglycerides or high-density lipoprotein cholesterol [HDL]), prospective data from studies such as the Framingham Heart Study suggest that a significant number of persons with low cholesterol levels may develop CAD[2–4] and that depressed HDL levels may contribute to the incidence of myocardial infarction or death from CAD,[5–9] particularly in this group.[10,11] Currently, no measurement of HDL is routinely recommended unless the total cholesterol is >6.21 mmol/liter (240 mg/dl) or in the presence of 2 risk factors for the development of CAD (or established CAD) when the cholesterol level is between 5.17 and 6.20 mmol/liter (200 and 239 mg/dl).[1,12]

In this report, we have defined a group of patients in whom CAD exists despite having low levels of total cholesterol. These patients are more likely to be men, have a family history of premature CAD, and have HDL levels ≤0.90 mmol/liter (35 mg/dl). Therefore we suggest that HDL measurement be considered in

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TABLE I Serum Lipids of Hospitalized Patients

Population	No. of Pts.	Age (years)	Cholesterol mmol/liter (mg/dl)	HDL mmol/liter (mg/dl)	Cholesterol/HDL	Triglycerides mmol/liter (mg/dl)
Total	2,535	60.9 (± 0.3)	5.42 ± 0.03 (210 ± 1)	1.04 ± 0.01 (40.2 ± 0.4)	5.7 ± 0.1	2.22 ± 0.10 (196 ± 9)
Men	1,563	58.5 (± 0.3)*	5.26 ± 0.03* (203 ± 1)	0.95 ± 0.01* (36.8 ± 0.4)	6.0 ± 0.1*	2.20 ± 0.15 (194 ± 13)
Women	972	64.8 (± 0.3)	5.69 ± 0.05 (220 ± 2)	1.18 ± 0.01 (45.6 ± 0.4)	5.4 ± 0.1	2.24 ± 0.13 (198 ± 12)

*Men versus women, $p < 0.001$.
All values are mean (mmol/liter) ± standard error of the mean.
HDL = high-density lipoprotein.

persons with desirable cholesterol levels who have established CAD as well as in men with a family history of early CAD.

METHODS

Beth Israel Hospital is served by a clinical computing system that routinely stores patient data as part of the process of patient care and facilitates investigator searches of this clinical data.[13] For this study all consecutive admissions during 1987 and 1988 (nonobstetric) were used for analysis so as to reduce the wide influence of the National Cholesterol Education Program guidelines (published in November 1988) on physician and patient practices.

From 1987 to 1988, 3,174 patients (10% of all admissions) had serum cholesterol measured within 48 hours of admission; 2,535 of these patients also had HDL determined at the same time. The fasting state was only guaranteed for patients in the population undergoing angiography (see later). The first admission for each of these 2,535 patients comprised the study group that was further analyzed.

In part 1 of the study, patients with an admission serum cholesterol value <5.17 mmol/liter (200 mg/dl) were divided into groups with and without the diagnosis of CAD. CAD was considered to be present when the patient had a discharge diagnosis of an acute or prior myocardial infarction, unstable angina or stable angina pectoris. In accordance with criteria for low HDL levels set forth by the National Cholesterol Education Program guidelines,[1] the group with cholesterol <5.17 mmol/liter (200 mg/dl) was subdivided into those with HDL < and ≥0.90 mmol/liter (35 mg/dl). A univariate analysis of additional cardiovascular risk factors was conducted. Age and sex of the patients, as well as the presence or absence of a discharge diagnosis of diabetes mellitus and systemic hypertension were available in the hospital database. A history of tobacco use, prescribed medications, and a family history of premature cardiovascular disease (defined as clinical CAD or cerebrovascular disease before the age of 55 years in a first-degree relative) were ascertained by chart review of a computer-generated random sample of 20% (n = 215) of the patients with cholesterol <5.17 mmol/liter (200 mg/dl).

In part 2 of the study, patients were selected on the basis of the presence or absence of CAD as assessed by coronary angiography. Coronary disease was considered present if ≥50% luminal stenosis was present in at least 1 major coronary vessel. All coronary cineangiograms were reviewed by ≥2 cardiologists and the number of diseased vessels and the location of luminal stenoses was recorded. Those with a significant coronary stenosis(es) were classified into 2 groups: those having total cholesterol values < and ≥5.17 mmol/liter (200 mg/dl). Patients who underwent angiography and who were admitted for purely elective procedures were analyzed as a separate subgroup. Again, such patients having cholesterol <5.17 mmol/liter (200 mg/dl) were classified into groups with and without CAD. Mean values for cholesterol, HDL, cholesterol/HDL ratio and triglycerides were calculated for these groups of patients and compared.

Lipid and lipoprotein measurements were performed as previously described.[14] Statistical comparison of the mean lipid values for different patient groups was accomplished using a 2-tailed Student's t test. Chi-square analysis was used to compare 2×2 proportions. Relative risk and confidence intervals at the 95% level were determined using a standard formula.[15]

RESULTS

Patient population: Mean total serum cholesterol for the study cohort of 2,535 as well as for the male and female subgroups is listed in Table I. These values were similar to those of the National Center for Health Statistics for the United States population (5.51 ± 0.04 mmol/liter [213 ± 2 mg/dl]) used in developing the National Cholesterol Education Program guidelines[16] and also similar to those found in the Lipid Research Clinics Prevalence Trial.[17] Of these 2,535 patients, 1,770 (70%) had CAD as a discharge diagnosis and

TABLE II Patient Characteristics in Cohorts With and Without Coronary Artery Disease with Total Cholesterol <5.17 mmol/liter (200 mg/dl) (n = 1,084)

	Coronary Artery Disease	
	Present (n = 690)	Absent (n = 394)
Mean age (± SEM)	63.4 (± 0.5)*	56.7 (± 0.9)
Men	524 (76%)‡	222 (56%)
Women	166 (24%)	172 (44%)
Diabetes mellitus	117 (17%)	53 (13%)
Systemic hypertension	198 (29%)	103 (26%)
Cigarette use†	78/140 (56%)	37/75 (50%)
Family history of premature CAD†	56/140 (40%)‖	3/75 (4%)
Lipid-lowering agents†	4/140 (3%)§	0/75 (0%)

*p <0.001; ‡chi-square = 44.88, p <0.001; ‖chi-square = 164.58, p <0.001; §chi-square = 12.33, p <0.001.
†Data obtained by chart review of a random sample of 20% (see text).
SEM = standard error of the mean.

765 (30%) did not. Of those having CAD, other diagnoses coexisting most frequently with CAD included essential hypertension, hypercholesterolemia, congestive heart failure, adult-onset diabetes mellitus, chest pain (unspecified), valvular heart disease, atrial and ventricular arrhythmias, and chronic obstructive airways disease.

Part 1: PREVALENCE OF CORONARY ARTERY DISEASE WITH LOW TOTAL SERUM CHOLESTEROL: Forty-two percent of the 2,535 patients (1,084) had a total cholesterol of <5.17 mmol/liter (200 mg/dl), a similar proportion as the general population.[16] Among these patients, the diagnosis of CAD was present in 690 (64%). The clinical risk factor characteristics of these patients are listed in Table II. Patients with low cholesterol levels who also had the diagnosis of CAD were predominantly men and had a significantly more frequent family history of CAD than those without CAD (p <0.001). A history of diabetes, hypertension and tobacco use were similar among the 2 groups. Lipid-lowering agents were used by 3% of the population in this group and in each case the drug was niacin.

Serum HDL levels <0.90 mmol/liter (35 mg/dl) were found in 60% of patients with CAD and total cholesterol values <5.17 mmol/liter (200 mg/dl), compared with 47% in the group without CAD and cholesterol values <5.17 mmol/liter (200 mg/dl) (Table III). The relative risk of having CAD with HDL <0.90 mmol/liter (35 mg/dl) and cholesterol <5.17 mmol/liter (200 mg/dl) was 1.20, 95% confidence interval = 1.09–1.30.

Table IV lists the mean lipid profiles of the population with total cholesterol <5.17 mmol/liter (200 mg/dl). Mean cholesterol was significantly higher for patients with than without CAD. Likewise, the mean serum HDL was significantly lower for those with than without CAD. Mean cholesterol/HDL ratio was significantly higher and >5.0 for patients with than without CAD.

TABLE III Hospitalized Patients with Total Cholesterol ≤5.17 mmol/liter (200 mg/dl): Coronary Artery Disease as a Function of High-Density Lipoprotein Threshold of 0.90 mmol/liter (35 mg/dl)

Part I: Coronary Artery Disease by Clinical Diagnosis

	Coronary Artery Disease	
	Present (n = 690)	Absent (n = 394)
HDL <0.90 mmol/liter (35 mg/dl)	414 (60%)	186 (47%)
HDL ≥0.90 mmol/liter (35 mg/dl)	192 (28%)	170 (48%)
Chi-square = 16.61; p <0.001		

Part II: Coronary Artery Disease by Angiography

	Coronary Artery Disease	
	Present (n = 424)	Absent (n = 86)
HDL <0.90 mmol/liter (35 mg/dl)	252 (59%)	41 (48%)
HDL ≥0.90 mmol/liter (35 mg/dl)	172 (41%)	45 (52%)
Chi-square = 4.04; p <0.05		

Part III: Elective Angiography

	Coronary Artery Disease	
	Present (n = 281)	Absent (n = 61)
HDL <0.90 mmol/liter (35 mg/dl)	180 (64%)	30 (49%)
HDL ≥0.90 mmol/liter (35 mg/dl)	101 (36%)	39 (51%)
Chi-square = 4.68; p <0.04		

HDL = high-density lipoprotein.

When the cohort with cholesterol <5.17 mmol/liter (200 mg/dl) was divided between men and women, similar statistically significant differences were observed in men with than without CAD (see Table IV). However, in women with CAD, only total cholesterol was significantly higher among those with than without CAD; the cholesterol/HDL ratio tended to be higher and levels of serum HDL tended to be lower in the group with CAD but this did not attain statistical significance.

Part 2: PREVALENCE OF LOW TOTAL SERUM CHOLESTEROL IN PATIENTS WITH CORONARY ARTERY DISEASE BY ANGIOGRAPHY: Of the 2,535 patients in the study cohort, 1,411 underwent coronary angiography, representing 52% of all coronary angiograms during the study period. Of this group, 1,197 patients had documented CAD and 214 had normal coronary arteries. Table III lists the distribution of high and low HDL among patients with and without CAD whose cholesterol was <5.17 mmol/liter (200 mg/dl). Thirty-two percent of patients (n = 424) with CAD had cholesterol <5.17 mmol/liter (200 mg/dl). Fifty-nine percent of these

TABLE IV Serum Lipids in Patients With and Without Coronary Artery Disease with Total Cholesterol <5.17 mmol/liter (200 mg/dl)

Population	No. of Pts.	Cholesterol mmol/liter (mg/dl)	HDL mmol/liter (mg/dl)	Cholesterol/HDL	Triglycerides mmol/liter (mg/dl)
+ CAD	690	4.39 ± 0.02* (170 ± 1)	0.93 ± 0.01* (36.0 ± 0.4)	5.1 ± 0.1*	1.76 ± 0.06† (155 ± 5)
− CAD	394	4.11 ± 0.04 (160 ± 2)	1.03 ± 0.02 (40.0 ± 0.8)	4.5 ± 0.1	1.54 ± 0.10 (136 ± 9)
Total	1,084				
Men	746				
+ CAD	524	4.39 ± 0.03* (170 ± 1)	0.89 ± 0.01* (34.4 ± 0.4)	5.3 ± 0.1*	1.81 ± 0.06 (160 ± 5)
− CAD	222	4.09 ± 0.05 (158 ± 2)	0.99 ± 0.03 (38.2 ± 1.2)	4.7 ± 0.1	1.66 ± 0.17 (147 ± 15)
Women	338				
+ CAD	166	4.39 ± 0.05* (170 ± 2)	1.05 ± 0.02 (40.6 ± 0.8)	4.5 ± 0.1	1.58 ± 0.13 (140 ± 12)
− CAD	172	4.15 ± 0.06 (161 ± 2)	1.09 ± 0.03 (42.1 ± 1.2)	4.3 ± 0.1	1.40 ± 0.10 (124 ± 9)

*p <0.001; †p <0.03.
All values are mean ± standard error of the mean.
CAD = coronary artery disease; HDL = high-density lipoprotein; + = present; − = absent.

TABLE V Serum Lipids of Patients Having Angiography and Total Cholesterol <5.17 mmol/liter (200 mg/dl)

Population	No. of Pts.	Cholesterol mmol/liter (mg/dl)	HDL mmol/liter (mg/dl)	Cholesterol/HDL	Triglycerides mmol/liter (mg/dl)
All angiography patients					
+ CAD	424	4.45 ± 0.03* (172 ± 1)	0.93 ± 0.06† (35.9 ± 0.5)	5.2 ± 0.1†	1.71 ± 0.06 (151 ± 5)
− CAD	86	4.33 ± 0.06 (168 ± 2)	1.03 ± 0.04 (39.9 ± 1.5)	4.6 ± 0.1	1.72 ± 0.16 (152 ± 14)
Elective patients					
+ CAD	281	4.48 ± 0.03* (174 ± 1)	0.90 ± 0.90* (34.9 ± 0.6)	5.3 ± 0.1†	1.66 ± 0.08 (147 ± 7)
− CAD	61	4.33 ± 0.07 (167 ± 3)	1.03 ± 0.04 (40.0 ± 1.7)	4.6 ± 0.2	1.73 ± 0.19 (153 ± 17)

*p <0.05; †p <0.01.
All values are mean ± standard error of the mean.
Abbreviations as in Table IV.

patients (n = 252) had HDL <0.90 mmol/liter (35 mg/dl) compared with 48% for patients without CAD.

Table V lists the mean values for cholesterol, HDL, total cholesterol/HDL ratio and triglycerides for all patients undergoing angiography who had a total cholesterol <5.17 mmol/liter (200 mg/dl). Mean total cholesterol was significantly higher, mean HDL was significantly lower, and cholesterol/HDL ratio was higher in those with than without CAD.

The angiographic characteristics (1 vessel vs multivessel disease) of patients with CAD were examined as a function of HDL levels and it appeared that the degree of disease was not related to levels of HDL (data not shown).

Prevalence of low total serum cholesterol in patients electively admitted for coronary angiography: Most patients (964, 68%) having angiography and who had total cholesterol and HDL measured were electively admitted for their procedure. In this subgroup of patients with angiography, 35% had cholesterol <5.17 mmol/liter (200 mg/dl). Eighty-two percent (281 of 342) had angiographically significant CAD; 18% had normal coronary arteries. Table III lists the distribution of HDL < and ≥0.90 mmol/liter (35 mg/dl) for the elective angiography patients having a cholesterol <5.17 mmol/liter (200 mg/dl) both with and without CAD. Sixty-four percent of those with CAD (180 of 281) had HDL <0.90 mmol/liter (35 mg/dl) compared to 49% for patients without CAD.

DISCUSSION

Although the National Cholesterol Education Program defines cholesterol <5.17 mmol/liter (200 mg/dl) as desirable, this threshold does not eliminate the possibility that CAD is present, and may not even protect against the development of CAD. In our retro-

spective observational analysis on a cohort of 2,535 patients admitted to Beth Israel Hospital in 1987 and 1988, we found several important features among these patients having lipid values measured: (1) Low admission serum cholesterol values (<5.17 mmol/liter [200 mg/dl]) are frequent; (2) CAD appears to be highly prevalent despite these patients having a low total serum cholesterol; (3) those having CAD and low levels of cholesterol are most frequently men, have a strong family history of premature CAD, and approximately two-thirds have levels of HDL <0.90 mmol/liter (35 mg/dl); and (4) even at low cholesterol levels, the absence of CAD is associated with a lower mean serum cholesterol.

We determined that a total cholesterol <5.17 mmol/liter (200 mg/dl) was present in 42% (1,084 of 2,535) of patients having serum cholesterol and HDL measurements on or shortly after admission. Among these patients the prevalence of CAD was 60%. This strikingly high prevalence of disease is undoubtedly due to selection bias favoring persons with suspected or established CAD. However, even considering the selection bias, the conclusion that important coronary disease exists even at "low" levels of total cholesterol or low-density lipoprotein cholesterol cannot be overlooked. Although we do not suggest that CAD is as prevalent in the general population with total cholesterol <5.17 mmol/liter (200 mg/dl) as in a hospitalized population, our data do suggest that having a total cholesterol <5.17 mmol/liter (200 mg/dl) does not free one from the risk of developing CAD. We and others[18] suggest that a false sense of security may be established in both the physician and the patient when a serum cholesterol <5.17 mmol/liter (200 mg/dl) is found.

Several factors may have reduced cholesterol levels in these patients including their medications and prior dietary interventions or counseling. However, only 3% of the patients with CAD were taking lipid-lowering agents; none of the patients without CAD were taking lipid lowering drugs at the time of cholesterol measurement. Other medications, e.g., β blockers and diuretics, were used more frequently in patients with CAD but most would tend to elevate serum cholesterol.[19] Prior dietary interventions, on the other hand, may have an impact on the cholesterol values obtained. Whereas dietary strategies are at the core of National Cholesterol Education Program and American Heart Association guidelines for the management of hypercholesterolemia, in order to minimize the potential impact of diet on the values for our population, data were collected for 1987 and 1988 before the publication of the National Cholesterol Education Program recommendations. We have no data on how many patients in our study received nutritional counseling before their 1987 or 1988 hospitalization, but it is known that this preceded the marked increase in cholesterol awareness that has occurred more recently.[20]

Cholesterol values may be affected by acute illness;[21] however, it appears that hospitalization, per se, and in particular hospitalization for patients undergoing coronary angiography has little effect on admission serum cholesterol values.[22] To exclude acute illness as a confounding variable in our hospital-based population, we examined the subgroup of relatively "healthy" patients admitted electively for angiography. The lipid data from this "usual health" group with CAD were strikingly similar to the nonelectively-admitted patients with CAD (Tables III and V): (1) cholesterol values <5.17 mmol/liter (200 mg/dl) were observed in approximately one-third of the sample, (2) 82% had CAD, and (3) 64% had HDL <0.90 mmol/liter. Significant differences in total cholesterol, HDL, and cholesterol/HDL ratio were found between those with and without CAD. Therefore our study population, although a select group of hospitalized patients, appears to have lipid values representative of an otherwise stable population of risk for having or having established CAD.

Given that these patients have CAD with low levels of cholesterol, it stands to reason that risk factors other than high levels of low-density lipoprotein contributed to their development of CAD. In this study, we have attempted to characterize the "high risk" patient with a low serum cholesterol. Other factors that were more frequently observed in the disease group were male gender and a family history of premature CAD (Table II) as well as low levels of HDL (<0.90 mmol/liter [35 mg/dl]).

Patients with desirable cholesterol levels and CAD had a 10-fold increase in the prevalence of a positive family history of premature CAD relative to patients with comparable cholesterol values and no CAD. In fact, the univariate statistic for family history (chi-square = 164.6, Table II) was substantially larger than that for HDL (chi-square = 16.6, Table III). Whereas other studies have found that family history is a weak predictor of CAD in populations with a broad range of cholesterol values, our findings suggest it is of particular importance in the subset of patients with cholesterol levels <5.17 mmol/liter (200 mg/dl).

The finding that HDL is a discriminator for CAD, even at low cholesterol levels, is not surprising. The initial report[3] from the Framingham Study demonstrating an inverse relation between HDL and the incidence of CAD was among the first such observations. Follow-up of that original cohort 12 years later confirmed the re-

lation at all levels of cholesterol.[4] In fact, HDL <1.03 mmol/liter (40 mg/dl) alone could account for nearly half the incidences of CAD regardless of the serum cholesterol. Data from the Physician's Health Study showed that the physicians who developed myocardial infarction had lower levels of HDL, when compared to a matched control cohort free of myocardial infarction. In fact, the mean serum cholesterol for both physicians in this study who had myocardial infarction and the control subjects was low (5.61 and 5.56 mmol/liter [217 and 215 mg/dl, respectively]), and there was no statistically significant difference in cholesterol values between the 2 groups.[23]

Because of the high frequency of low serum cholesterol among hospitalized patients and their high prevalence of CAD, we suggest caution in applying the National Cholesterol Education Program guidelines to hospitalized patients, and conversely, if those guidelines are to be applied, hospitalization should not be used as a time to screen for coronary risk. Although the true incidence of CAD in persons with low cholesterol levels is lower than that for hospitalized patients (for reasons previously cited), the data presented would suggest that a high-risk group of patients with serum cholesterol <5.17 mmol/liter (200 mg/dl) may be identified as men with a family history of premature CAD and having HDL <0.90 mmol/liter (35 mg/dl). Whether or not aggressive treatment strategies to reduce cholesterol, increase HDL and decrease the cholesterol/HDL ratio in this group of patients may reduce the incidence of CAD remains undetermined at the present time.

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Late Follow-Up After Repair of Left Ventricular Aneurysm and (Usually) Associated Coronary Bypass Grafting

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This study assesses clinical and operative data on a large group of patients in whom a left ventricular (LV) aneurysm was repaired to determine factors that might predict in-hospital and long-term outcome. Long-term follow-up study was obtained in 296 of 298 patients undergoing LV aneurysm repair with or without coronary artery bypass grafting between 1974 and 1986. No patient had sustained a myocardial infarction within 2 weeks of surgery or was undergoing other concurrent cardiac surgery. The average age of the study patients was 57 ± 9 years and the average ejection fraction was 35 ± 13%. Ninety percent of the patients underwent concurrent bypass grafting, with an average of 2.2 ± 1.3 grafts placed. Fourteen (5%) patients died in the hospital, with most deaths attributable to LV dysfunction. Advanced age and less extensive revascularization were correlates of in-hospital mortality. The 10-year survival was 57%, myocardial infarction-free survival 43%, and freedom from death, myocardial infarction and reoperative coronary surgery 41%. Advanced age, systemic hypertension, significant left main coronary artery narrowing and emergent operative status were multivariate correlates of long-term mortality. A low-risk population was defined by the absence of these risk factors, and high-risk by the presence of ≥1 risk factors. The 10-year survival was 71% in the low-risk and 41% in the high-risk groups ($p = .0006$). The 10-year myocardial infarction free survival was 55% in the low-risk and 31% in the high-risk groups ($p = 0.0017$). LV aneurysm repair may be performed with acceptable in-hospital mortality, and the long-term risk may be stratified. However, in the absence of controlled studies, uncertainty remains as to the appropriate patients for LV aneurysm repair.

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The first successful left ventricular (LV) aneurysmectomy was reported >30 years ago by Likoff and Bailey.[1] Although occasionally performed as an isolated cardiac surgical procedure, it is most often performed concurrently with coronary artery bypass grafting.[2–6] The proponents of LV aneurysm repair claim that the benefits in appropriately selected patients include relief of symptoms of congestive heart failure, reduction of anginal symptoms, ablation of arrhythmogenic foci and removal of LV thrombi.[7,8] Questions concerning the efficacy of LV aneurysm repair have resulted in a decline in its use.[2,9] Evidence documenting objective improvement in LV function with LV aneurysm repair is sparse, and benefit has not been consistently reported.[10–17] One large series suggested that coronary arterial revascularization may be largely responsible for the improved outcome seen with concurrent LV aneurysm repair.[4] In several studies, conjecture arises as to whether those with the poorest preoperative LV global function, who are subject to the highest perioperative mortality, might also benefit most from LV aneurysm repair.[3,18] Whereas variables associated with in-hospital[2,5,6,8,11,19–22] and long-term[4,6,11,19,22–27] survival have been suggested, there remains considerable uncertainty as to the place of this procedure. To further define the place of LV aneurysm repair, this report reviews the perioperative and long-term outcome in a large series of well-defined patients undergoing this operation at our institution between 1974 and 1986.

METHODS

Patients: There were 357 patients who had either LV aneurysmectomy or LV plication performed for true LV aneurysms between 1974 and 1986. An angiographic diagnosis of LV aneurysm was made when there was a localized protrusion of the LV cavity during systole without inward systolic contraction; a surgical diagnosis was made intraoperatively at the discretion of

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the surgeon. To eliminate confounding factors, we excluded patients who had sustained a myocardial infarction within 2 weeks of surgery (by electrographic or cardiac enzyme criteria), required repair or replacement of a cardiac valve, required repair of LV septal defect, or had electrophysiologic study-guided endocardial resection performed during the same operation. This reduced the study group to 298 patients, 296 of whom we were able to obtain long-term follow-up.

Definitions: Preoperative clinical data analyzed included age, gender, systemic hypertension, diabetes mellitus, angina class, congestive heart failure class, LV ejection fraction, number of coronary vessels with significant obstruction, history of prior surgical revascularization, indication for operation and elective versus emergent operative status. Hypertension and diabetes were determined from the history. Congestive heart failure was graded by the New York Heart Association classification. A history of congestive heart failure was deemed present if there was class II to IV failure. Angina pectoris was graded by the Canadian Cardiovascular Society classification. LV ejection fraction was ascertained from contrast angiograms performed at our institution in 223 patients, and was determined from catheterization, radionuclide or echocardiographic assessment from referring institutions in 57 patients; preoperative estimate of LV systolic function was unavailable in only 19. A coronary artery was considered significantly obstructed if it or 1 of its large branches had ≥50% diameter narrowing.

Operative indications were based on the following criteria: (1) angina — appropriate clinical history or stenosis of vessels supplying viable myocardium, or both; (2) congestive heart failure — appropriate clinical history or ejection fraction <35%, or both; (3) thrombectomy — detection of thrombus on angiographic or echocardiographic assessment; and (4) LV arrhythmia — LV arrhythmia, usually LV tachycardia or fibrillation, which the attending cardiologist believed might respond to aneurysm repair or revascularization, or both. An operation was considered emergent if performed on the day of the diagnostic catheterization or if the clinical situation mandated early surgery. Perioperative factors analyzed included use of systemic hypothermia without aortic cross-clamping, myocardial infarction, cerebrovascular event, and use of an intraaortic balloon pump in the postoperative period. A postoperative myocardial infarction was determined by development of new electrocardiographic Q waves of ≥0.04 second duration or characteristic changes of the cardiac enzymes with persistent T-wave inversion. Occurrence of a postoperative cerebrovascular event was determined by the appearance of new neurologic abnormalities.

Operative technique: The operative technique used for coronary artery bypass grafting has been previously described.[28] Determination of the type of repair procedure, plication or aneurysmectomy, was dictated by the surgical findings. For smaller LV aneurysms without significant pericardial adhesions, plication of the aneurysmal portion was performed between 2 Teflon® strips to exclude the aneurysm from the LV cavity. Aneurysmectomy was performed on larger aneurysms, with evacuation of thrombotic material and excision of the fibrotic aneurysmal rim to within approximately 2 cm of the base of the papillary muscles. To assure hemostasis at the ventriculotomy site, a 3-layer closure was usually performed. Aortic cross-clamping and myocardial preservation were used when concomitant coronary bypass grafting was performed with plication or aneurysmectomy. When either type of aneurysm repair was performed without concurrent bypass grafting, systemic hypothermia to 28°C was used without aortic cross clamping.

Data collection and analysis: All data were collected prospectively on standard database forms and entered into a computerized database. These forms included historical, physical examination, catheterization and operative data, as well as data on the hospital course. Long-term follow-up data were obtained by telephone questionnaire of the patients, family members or referring physicians. All data are expressed as mean ± standard deviation for continuous variables and as proportions for discrete variables. Continuous variables were compared by unpaired *t* tests, and discrete variables by chi-square. Survival estimates for the various patient groups were determined by the Kaplan-Meier method.[29] Significant differences in survival curves were tested by the Mantel-Cox method.[30] The Cox proportional-hazards model[31] was used to assess the significance of multiple variables in long-term events and mortality.

RESULTS

Clinical profile: Between 1974 and 1986, repair of an LV aneurysm was performed in 298 patients without recent myocardial infarction, concomitant valvular or LV septal defect repair, or electrophysiologic study-guided endocardial resection. Clinical characteristics are presented in Table I. The average age of these patients was mean ± standard deviation 57 ± 9 years, and 81% were men. Hypertension was noted in 32% and diabetes in 14%. Slightly <50% had a clinical history of congestive heart failure. Ejection fraction evaluations were available in 279 patients (mean value 35 ± 13%), and 60% had an ejection fraction <35%. Two hundred twelve patients had severe angina and 69% had grade III or IV angina. Angiographic assess-

TABLE I Clinical Characteristics

	All Repairs	Aneurysmectomy	Plication	p Value
	298 (100%)	215 (72%)	83 (28%)	
Age (years)	57 ± 9	57 ± 8	58 ± 10	NS
Age > 65 years	56 (19%)	36 (17%)	20 (24%)	0.14
Men	243 (81%)	174 (81%)	69 (83%)	NS
Systemic hypertension	94 (32%)	65 (30%)	29 (35%)	NS
Diabetes mellitus	28 (14%)	17 (11%)	11 (22%)	NS
CHF	139 (47%)	110 (51%)	29 (35%)	0.01
Ejection fraction	35 ± 13	33 ± 13	38 ± 14	0.01
Ejection fraction < 35%	166 (60%)	131 (64%)	35 (46%)	0.005
Angina class III to IV	147 (69%)	103 (66%)	44 (79%)	0.08
Coronary arteries narrowed ≥ 50% in diameter				
1	49 (16%)	41 (19%)	8 (10%)	
2	96 (32%)	74 (34%)	22 (26%)	0.03
3	139 (47%)	92 (43%)	47 (57%)	
Left main	14 (5%)	8 (4%)	6 (7%)	
Indication				
AP alone	62 (21%)	36 (17%)	26 (31%)	
CHF alone	24 (8%)	23 (11%)	1 (1%)	0.001
AP and CHF	212 (71%)	156 (73%)	56 (68%)	
Emergency	20 (7%)	18 (8%)	2 (2%)	0.06

Ejection fraction data available on 279 patients, 203 with aneurysmectomy and 76 with plication; angina classification available on 212 patients, 156 with aneurysmectomy and 56 with plication; hypertension data available on 297 patients. Indications as described in text.
AP = angina pectoris; CHF = congestive heart failure; NS = not significant.

TABLE II Operative Data

	All Repairs	Aneurysmectomy	Plication	p Value
Associated coronary bypass surgery	269 (90%)	187 (87%)	82 (99%)	0.001
No. of grafts	2.2 ± 1.3	2.0 ± 1.3	2.8 ± 1.1	0.0001
Internal mammary artery graft	26 (9%)	19 (9%)	7 (8%)	NS
Intraaortic balloon pump	34 (11%)	31 (14%)	3 (4%)	0.008
Cross-clamp utilized	280 (94%)	198 (92%)	82 (99%)	0.03
In-hospital mortality	14 (5%)	12 (6%)	2 (2%)	NS
Myocardial infarction	10 (3%)	5 (2%)	5 (6%)	0.11
Cerebrovascular event	6 (2%)	4 (2%)	2 (2%)	NS

NS = not significant.

ment was available in all 298 patients, and most had either 2- or 3-vessel disease; only 16% had 1-vessel disease and 5% had left main disease. The frequency of the 2 most common indications for surgery, angina and congestive heart failure, are listed in Table I; 71% of patients had both angina and congestive heart failure as indications. Thrombectomy, LV arrhythmias and pericardectomy were never the sole indications, and as concomitant indications, occurred in 19, 16 and 1 patient, respectively. The operation was emergent in 7%. Prior myocardial infarctions were documented in 97%, and all aneurysms were the consequence of ischemic heart disease. Only 2% of the patients had undergone prior coronary surgery.

Most aneurysms (72%) were repaired by aneurysmectomy (Table I), either because of large size or to perform concurrent thrombectomy. Patients undergoing plication when compared with those undergoing aneurysmectomy were less likely to have a history of congestive heart failure and had a higher mean ejection fraction. Patients who underwent repair by means of plication had significantly more severe coronary artery disease (64% with 3-vessel or left main disease vs 47%). The plication group had angina as the indication for the procedure to be performed more frequently, congestive heart failure as the indication for the procedure to be performed less frequently; they also tended to have more severe angina. Patients with aneurysmectomy tended to undergo more frequent emergency surgery.

Operative data: Operative data are listed in Table II. Approximately 90% of patients had concomitant coronary bypass grafting with their aneurysm repair, including 9% who had an internal mammary graft. The average number of bypass grafts placed was 2.2 ± 1.3. LV dysfunction requiring the intraaortic balloon pump in the immediate postoperative period occurred in 11%. Systemic hypothermia was used in preference to aortic cross-clamping in only 6%. The patients undergoing plication were more likely to have concomitant revascularization and had more coronary grafts placed. The intra-

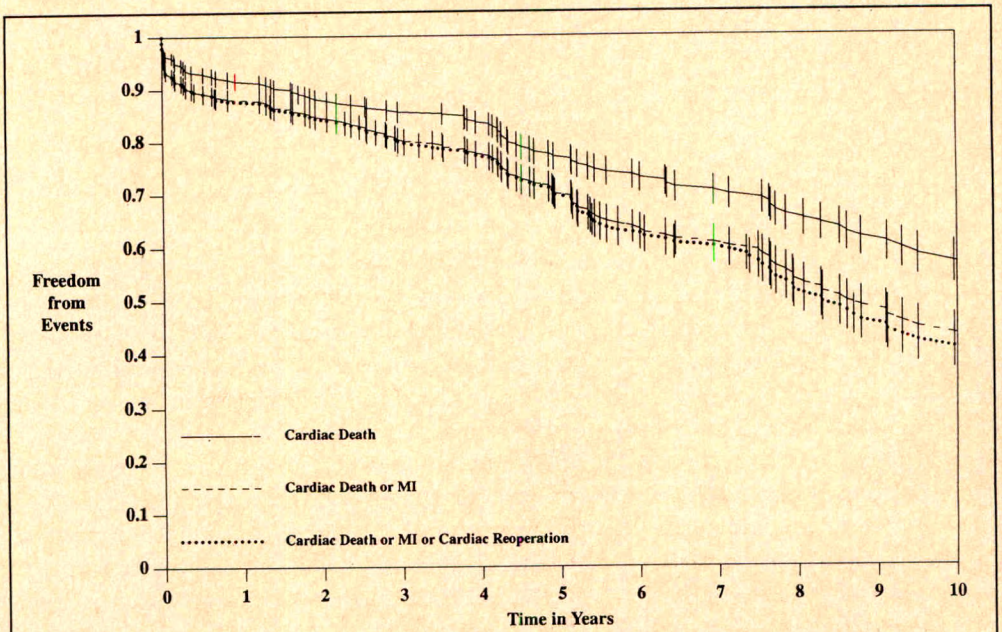
TABLE III Correlates of Long-Term Survival

	Survival		Univariate		Multivariate		
	5 Years	10 Years	Chi-Sq	p Value	Chi-Sq	p Value	Coefficient
Age <65 years	0.80	0.59	7.40	0.006	6.75	0.009	0.035
Age ≥65 years	0.72	0.49					
Hypertension absent	0.79	0.63	6.11	0.01	7.37	0.007	0.626
Hypertension present	0.71	0.42					
1 to 3 vessels diseased	0.79	0.59	4.34	0.04	6.47	0.01	0.275
Left main disease	0.50	0.29					
Elective surgery	0.79	0.61	3.23	0.07	4.00	0.05	0.375
Emergent surgery	0.51	0.26					
Ejection fraction ≥30	0.77	0.61	2.91	0.09	NS		
Ejection fraction <30	0.76	0.48					

Chi-Sq = chi-square test; NS = not significant.

aortic balloon pump was required more frequently in the aneurysmectomy group, which is consistent with more severe LV systolic dysfunction preoperatively. The plication group also was significantly less likely to undergo systemic hypothermia, probably because revascularization requires aortic cross-clamping. In-hospital mortality for our patients was 5%. Ten patients (3%) had postoperative myocardial infarctions (8 Q-wave infarctions) and 6 (2%) had postoperative cerebrovascular events.

There were 14 in-hospital deaths, 9 due to LV failure. Less common causes of death included arrhythmias, cerebrovascular events and multisystem organ failure. Only advanced age and the number of grafts placed at surgery were significant correlates of in-hospital mortality. The average age of patients dying in the hospital was 62 ± 8 years, compared with 57 ± 9 for those discharged ($p = 0.05$). The in-hospital mortality in patients aged <65 years was 4 vs 9% for those aged ≥65 ($p = 0.10$). Hospital survivors had an average of



Cardiac Death											
n Remaining	296	270	253	220	205	166	129	107	81	64	39
FF Events	1	.92	.88	.86	.84	.77	.74	.71	.66	.62	.57
Events	0	25	35	42	47	62	69	74	80	85	89
Cardiac Death or MI											
n Remaining	296	260	243	213	188	151	112	93	67	53	33
FF Events	1	.88	.85	.80	.78	.70	.64	.61	.54	.49	.43
Events	0	35	45	57	64	81	94	99	108	114	119
Cardiac Death or MI or Cardiac Reoperation											
n Remaining	296	259	242	212	187	151	111	92	66	53	33
FF Events	1	.88	.84	.80	.77	.70	.63	.60	.52	.46	.41
Events	0	36	46	58	65	82	96	101	112	119	124

FIGURE 1. Ten-year freedom from (FF) events of death, death or recurrent myocardial infarction (MI), and death, recurrent MI or cardiac reoperation, respectively. *Vertical bars on lines* represent standard error.

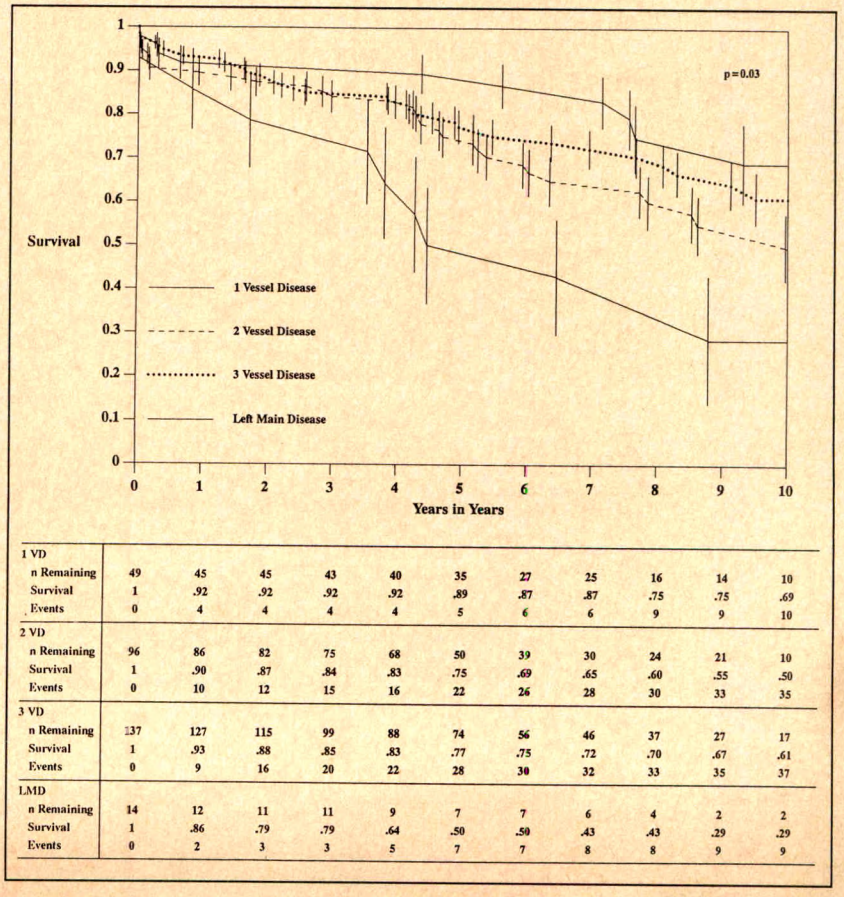
TABLE IV Correlates of Long-Term Myocardial Infarction-Free Survival

	Myocardial Infarction-Free Survival		Univariate		Multivariate		
	5 Years	10 Years	Chi-Sq	p Value	Chi-Sq	p Value	Coefficient
Elective surgery	0.79	0.61	9.57	0.002	9.57	0.002	0.4359
Emergent surgery	0.51	0.26					
Hypertension absent	0.73	0.49	5.29	0.02	6.41	0.01	0.5098
Hypertension present	0.64	0.29					
Age <65 years	0.73	0.45	3.85	0.05	3.94	0.05	0.0225
Age ≥ 65 years	0.56	0.39					
Ejection fraction ≥ 30	0.70	0.50	3.10	0.08	NS		
Ejection fraction <30	0.70	0.33					

Abbreviations as in Table III.

2.3 ± 1.3 grafts placed, compared with 1.6 ± 1.2 in those dying in the hospital ($p = 0.04$). A trend was noted toward poorer in-hospital survival in patients without concomitant revascularization (10%) compared with patients with associated revascularization (4%, $p = 0.13$). A trend was also noted toward increased in-hospital mortality in women (9%) compared with men (4%, $p = 0.09$).

Long-term prognosis: Late survival, survival without recurrent myocardial infarction (myocardial infarction-free survival), or need for cardiac reoperation (event-free survival) for all patients are shown in Figure 1. The actuarial survival, myocardial infarction-free survival and event-free survival were 57, 43 and 41%, respectively, at 10 years. A subsequent cardiac operation was required in 17 patients; 14 underwent reoperative coronary artery bypass grafting, 2 cardiac transplantation and 1 electrophysiologic study-guided endocardial resection. One patient undergoing reoperative coronary bypass surgery had concurrent mitral valve replacement, and another patient undergoing reoperative coronary bypass surgery had subsequent placement of an Automatic Implantable Cardioverter-Defibrillator. The major clinical and operative variables were examined as univariate and multivariate correlates of long-term survival (Table III). Advanced age, hypertension and more severe coronary artery disease were univariate correlates of less favorable long-term surviv-



1 VD											
n Remaining	49	45	45	43	40	35	27	25	16	14	10
Survival	1	.92	.92	.92	.92	.89	.87	.87	.75	.75	.69
Events	0	4	4	4	4	5	6	6	9	9	10
2 VD											
n Remaining	96	86	82	75	68	50	39	30	24	21	10
Survival	1	.90	.87	.84	.83	.75	.69	.65	.60	.55	.50
Events	0	10	12	15	16	22	26	28	30	33	35
3 VD											
n Remaining	237	127	115	99	88	74	56	46	37	27	17
Survival	1	.93	.88	.85	.83	.77	.75	.72	.70	.67	.61
Events	0	9	16	20	22	28	30	32	33	35	37
LMD											
n Remaining	14	12	11	11	9	7	7	6	4	2	2
Survival	1	.86	.79	.79	.64	.50	.50	.43	.43	.29	.29
Events	0	2	3	3	5	7	7	8	8	9	9

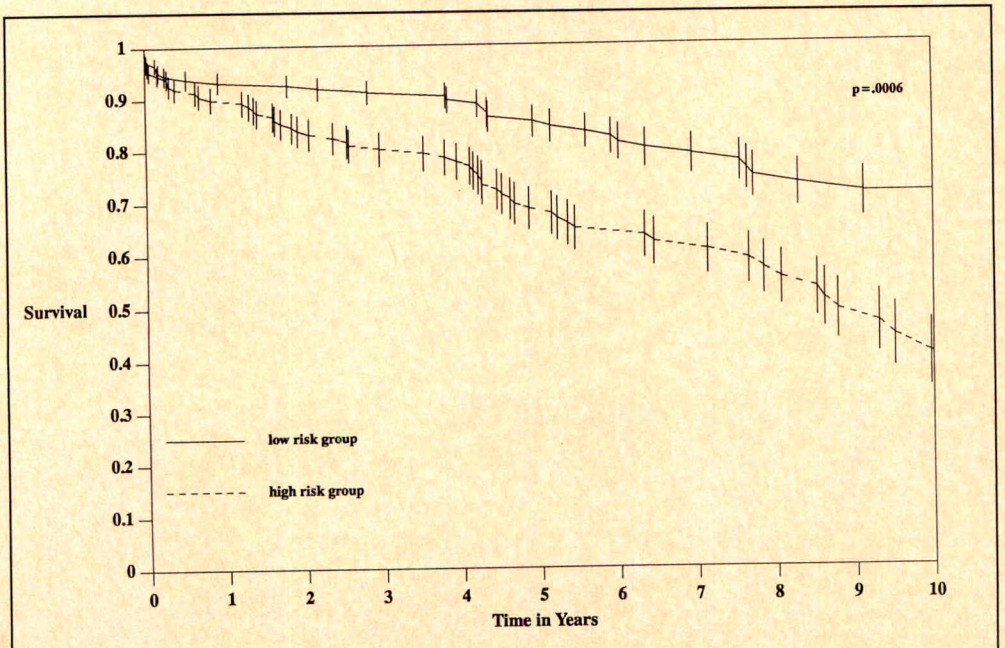
FIGURE 2. Survival for patients with 1-, 2- and 3-vessel disease (VD), and left main coronary artery disease (LMD), respectively.

al. Emergent surgery and more severe LV dysfunction trended toward decreased long-term survival. Advanced age, hypertension, more severe coronary artery disease and emergent surgery were multivariate correlates of worse long-term survival. Ejection fraction was not a multivariate correlate of survival. Gender, diabetes, the number of grafts placed, the type of repair and the surgical indication did not predict survival. Similarly, the major clinical and operative variables were examined as univariate and multivariate correlates of long-term myocardial infarction-free survival (Table IV). Emergent surgery, hypertension and advanced age were univariate correlates of less favorable long-term myocardial infarction-free survival, with a low ejection fraction a borderline correlate. Emergent surgery, hypertension and advanced age were multivariate correlates of worse long-term myocardial infarction free survival. Gender, diabetes, the number of vessels diseased, the number of grafts placed, the type of repair and the surgical indication did not predict myocardial infarction-free survival.

Survival assessed by the number of vessels diseased is presented in Figure 2. Whereas actuarial survival was similar for patients with 1-, 2- and 3-vessel disease (0.69, 0.50, and 0.61 at 10 years, respectively, with a 0.59 survival for the aggregate of the 3 groups), survival was significantly worse for patients with left main disease (0.29 at 10 years). The results of the analyses presented in Tables III and IV were used to define low- and high-risk groups. Risk was considered low if the patient was <65 years, the surgery was elective, left main coronary disease was absent and the patient was not hypertensive. Survival in the low- and high-risk groups is displayed in Figure 3. In 147 low-risk patients, survival at 5 years was 0.85, and at 10 years 0.71. In 149 high-risk patients, survival at 5 years was 0.69, and at 10 years 0.41. Myocardial infarction-free survival in the low- and high-risk groups is displayed in Figure 4. In 147 low-risk patients, myocardial infarction-free survival at 5 years was 0.79, and at 10 years 0.55. In 149 high-risk patients, myocardial infarction-free survival at 5 years was 0.61, and at 10 years 0.31.

DISCUSSION

LV aneurysm repair gained popularity because of the poor outcome of medically treated patients with LV aneurysms noted in early clinical and pathologic series.[1,6] However, a recent review stressed that many patients with LV aneurysms can be treated medically with careful attention to hemodynamics.[32] Owing to uncertain indications for LV aneurysm repair and lack of a large controlled trial of LV aneurysm repair, review of patient outcome after LV aneurysm repair remains the only method of assessing its clinical value. The interpretation of clinical series will be limited by



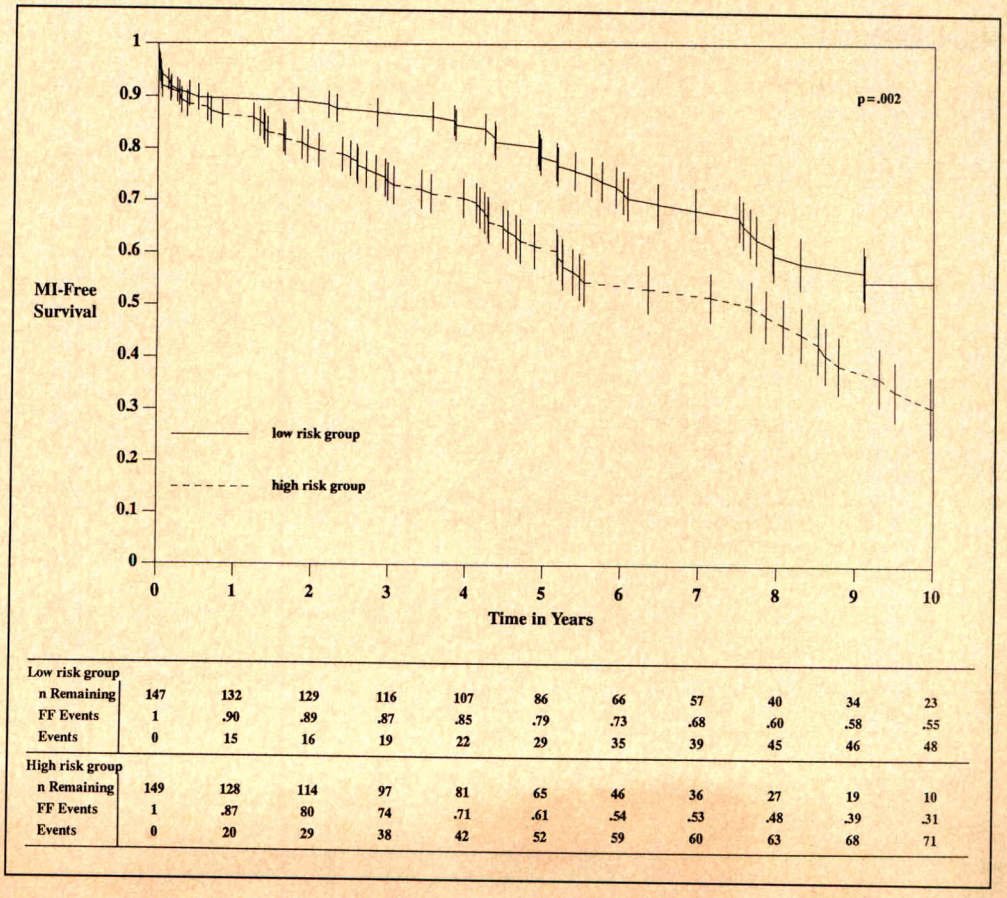
Low risk group											
n Remaining	147	137	134	122	114	92	74	65	50	41	27
Survival	1	.93	.93	.91	.90	.85	.82	.79	.75	.73	.71
Events	0	10	11	13	15	20	23	26	29	30	31
High risk group											
n Remaining	149	133	119	106	91	74	55	42	31	23	12
Survival	1	.90	.84	.80	.78	.69	.65	.62	.57	.49	.41
Events	0	15	24	29	32	42	46	48	51	55	58

FIGURE 3. Survival for low- and high-risk patients.

the definition used to diagnose an aneurysm, as well as on the indication for surgery. It should be appreciated that patients receiving LV aneurysm repair generally have multivessel coronary artery disease and poor LV function, and thus are at high risk for cardiac events.

The 298 patients in this report had a 5% in-hospital mortality, and 77 and 57% actuarial 5- and 10-year survival, respectively; this was despite the presence of multivessel coronary artery disease in 84% and an ejection fraction <35 in 60%. In other studies of LV aneurysm repair in ≥100 patients, 2 to 19% perioperative mortality and 57 to 78% actuarial survival at 5- to 10-year follow-up were reported.[3–6,10,19,23–27,33] In this series, mortality and cardiac events occurred more frequently early in the follow-up period, but continued to be seen throughout follow-up, as may be anticipated in patients with multivessel coronary artery disease and severe LV dysfunction. Assessment of numerous clinical and operative factors revealed that only advanced age and a smaller number of coronary bypass grafts predicted in-hospital mortality. Increased perioperative mortality with advanced age has also been observed by Cosgrove et al.[2] The significantly lower number of bypass grafts seen in those with in-hospital mortality may reflect a consequence of incomplete revascularization as noted by Najafi et al.[8] The severity of coronary artery disease, LV dysfunction, operative indication and emergent operative status were not noted to be correlates of in-hospital mortality as reported by other investigators.[2,5,8,19,22] The failure of several of these variables to predict in-hospital mortality may be due to the exclusion of patients with acute myocardial infarctions, or those requiring valvular or LV septal defect repair who tend to have a high perioperative mortality. In addition, the method used to assess LV function and the criteria used to define operative indications may differ from previous studies.

Advanced age, presence of hypertension, left main coronary artery disease and emergent operative status were correlated with less favorable long-term survival in this study. This permitted the definition of a low-risk group of patients aged <65 years without left main disease or hypertension who underwent elective surgery and had a 71% 10-year survival. The presence of ≥1 adverse factors placed the patient in a high-risk group with 41% 10-year survival, approximately twice the 10-year mortality of the low-risk group. Whereas advanced age, extent of coronary artery disease and emergent operative status have been previously reported as predictors of perioperative mortality,[2,5,8,19,22] only emergent surgery has previously been reported as a predictor of long-term mortality. Several studies have found LV dysfunction to be a univariate correlate of mortality.[4,6,20,22,24,26,27,33,34] Several studies have shown



Low risk group											
n Remaining	147	132	129	116	107	86	66	57	40	34	23
FF Events	1	.90	.89	.87	.85	.79	.73	.68	.60	.58	.55
Events	0	15	16	19	22	29	35	39	45	46	48
High risk group											
n Remaining	149	128	114	97	81	65	46	36	27	19	10
FF Events	1	.87	80	74	.71	.61	.54	.53	.48	.39	.31
Events	0	20	29	38	42	52	59	60	63	68	71

FIGURE 4. Myocardial infarction-free (MI-Free) survival for low- and high-risk patients. FF = freedom from.

that dysfunction outside of the aneurysmal zone correlated with mortality.[19,33,34] LV dysfunction may have failed to predict long-term mortality in the present study due to the relatively homogeneous group of patients with severe LV dysfunction. Several other studies have examined multivariate predictors of late mortality.[4,19,26] The registry from the Coronary Artery Surgery Study[4] found a congestive heart failure score, emergent surgery, the duration of chest pain, cardiac enlargement on x-ray, mitral regurgitation and other illnesses to correlate with late mortality. This study also compared survival with medically treated patients. Survival after aneurysmectomy was better than survival with medical therapy in patients with 3-vessel disease. The investigators point out that even in this study, selection of 1 form of therapy limits its use as a guide to appropriate therapy.[4]

Study limitations: The major limitation of this study is uncertainty in defining how patients are selected for LV aneurysm repair. This also makes it difficult to define a control group of patients. Thus, in the absence of a randomized trial, it may be difficult to know in which patients aneurysmectomy would be beneficial. In addition, the diagnosis of a myocardial infarction at follow-up is weak. Nonetheless, this study does provide improved ability to define immediate and long-term outcome.

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Seismocardiographic Changes Associated with Obstruction of Coronary Blood Flow During Balloon Angioplasty

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Seismocardiography, a new noninvasive technique, detects low-frequency cardiac vibrations on the chest wall during ventricular contraction and during both early and late ventricular filling. To evaluate the ability of seismocardiography to detect ischemia caused by decreased coronary blood flow, 35 patients were studied during coronary angioplasty. Seismocardiograms and electrocardiograms were recorded twice at baseline, with the catheter across the lesion before first inflation (n = 15), every 30 seconds during the first inflation, 1 and 2 minutes after the first inflation and ≥5 minutes after the final inflation. For comparison, sequential seismocardiograms were also obtained from 15 healthy volunteers. Electrocardiograms were blindly scored for ST change from baseline (0 = none, 1 = 0.5 mm ST depression, 2 = ≥1.0 mm ST depression, 3 = ST elevation). Seismocardiograms were blindly scored for change from baseline (0 = none, 1 = mild, 2 = moderate, 3 = marked) for both the systolic and diastolic waves. The average maximal systolic seismocardiographic score was 2.5 ± 0.8 for patients who had undergone angioplasty and 1.0 ± 0.9 for volunteers (p <0.001). The average maximal diastolic seismocardiographic score was 2.3 ± 0.8 for angioplasty patients and 0.7 ± 0.9 for volunteers (p <0.001). The percentage of angioplasty patients with electrocardiographic, systolic and diastolic seismocardiographic scores ≥2 was, respectively: 0, 11 and 14% at second baseline; 23, 67 and 53% with catheter across the lesion; 44, 75 and 59% after 30 seconds of inflation; 42, 71 and 61% after 60 seconds of inflation; 23, 74 and 61% after 1 minute of deflation; and 0, 71 and 47% 5 minutes after final inflation. The percentage of volunteers with seismocardiographic score ≥2 never exceeded 13% for systole or 14% for diastole at any time point.

Thus, both electrocardiograms and seismocardiograms changed rapidly during coronary angioplasty, whereas seismocardiograms did not change in volunteers. Most changes developed when the catheter crossed the lesion, before balloon inflation. These findings are consistent with the hypothesis that the seismocardiographic changes are due to ischemic changes in ventricular wall motion or compliance. Seismocardiographic changes persisted longer than electrocardiographic changes, possibly due to delayed recovery in ventricular function.

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Seismocardiography is a new noninvasive test for myocardial ischemia based on technology from the field of seismology.[1] The method measures low-frequency cardiac vibrations transmitted to the chest wall and attempts to detect changes in these vibrations in response to ischemia. Seismocardiography is a form of displacement cardiography, the general field of techniques that record movement of the body in response to cardiac motion. The concept underlying the use of displacement cardiography for detecting myocardial ischemia is that ischemia will produce a change in systolic or diastolic left ventricular wall motion that will result in a change in displacement. Other types of displacement cardiography include apexcardiography,[2] kinetocardiography,[3] ballistocardiography[4,5] and cardiokymography.[6,7] The resting seismocardiogram remains stable over ≥3 months in the absence of heart disease.[1] There is an identifiable normal wave pattern that is permanently altered by left bundle branch block, myocardial infarction, dilated cardiomyopathy, and reversibly altered by ventricular pacing.[1] Transient

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myocardial ischemia occurs during percutaneous transluminal coronary angioplasty as demonstrated by electrocardiography and by studies of left ventricular performance.[8–15] Therefore, angioplasty provides an opportunity to evaluate the effect of ischemia, produced by obstruction of coronary blood flow, on the seismocardiographic waves.

METHODS

Patients: Patients were recruited for this study who were undergoing elective percutaneous transluminal coronary angioplasty. We excluded patients who were undergoing emergency angioplasty or angioplasty during acute myocardial infarction. All patients signed informed consent. The angioplasty protocol was approved by the Investigational Review Board of Abbott Northwestern Hospital on March 11, 1988. For comparison, we obtained recordings from healthy volunteers who had no cardiac disease and were taking no medications. Each of these volunteers also signed informed consent. The volunteers' protocol was approved by the Investigational Review Board of Hennepin County Medical Center on March 31, 1988.

Angioplasty protocol: Angioplasty was performed using the standard technique. The initial balloon inflation was routinely performed for 1 to 1½ minutes, after which the balloon was deflated for at least 1 minute before the next inflation. The data for this study were recorded during the first balloon inflation.

Seismocardiography: The seismocardiographic equipment includes an ultra low-frequency, highly sensitive piezoelectric accelerometer (linear response 0.3 to 800 Hz, sensitivity 1.0 V/g) and a single-channel electrocardiogram used for signal timing. The accelerometer signal is processed through a 6 db/octave bandpass filter with corner frequencies at 0.3 and 50 Hz. The signals from the accelerometer and the electrocardiographic lead are digitized (sample rate 250/second) and stored on a microprocessor for subsequent analysis and printing.[1] Seismocardiographic recordings are obtained by placing the accelerometer on the sternum in the midline with the lower edge of the detector just above the xyphoid process. For this study, a minimum of 10 seconds of data were collected during each recording for signal processing. All recordings were obtained during normal quiet respiration. The seismocardiogram contains waves that correlate with aortic and mitral valve opening and closing and with left ventricular filling and ejection (Figure 1).

The seismocardiographic recordings were obtained from the angioplasty patients twice at baseline before the angioplasty catheter was placed in the coronary artery, and then with the balloon across the lesion before inflation when possible, every 30 seconds during balloon inflation, every minute during the first balloon deflation, and after ≥5 minutes following the final balloon inflation. The volunteers had recordings obtained at baseline, and then 1 hour, 1 day, 1 week, and 1 and 3 months after baseline. Each of the volunteers' recordings were obtained in the supine position after a brief rest period.

The seismocardiograms were signal-averaged for 10 cardiac cycles to reduce noise. The first (baseline) seismocardiographic recording of each angioplasty patient and volunteer was labeled, and the rest of that person's recordings were arranged randomly and blindly for comparison with the baseline recording. The sets of recordings from patients and volunteers were randomly mixed. One interpreter read each set of recordings as a unit. Data analysis involved visual inspection of the systolic and diastolic seismocardiographic waves separately. Each recording was scored for change from baseline: 0 = no change, 1 = slight change, 2 = moderate change, and 3 = marked change. This was done separately for both systolic and diastolic seismocardiographic changes. In a study of exercise seismocardiog-

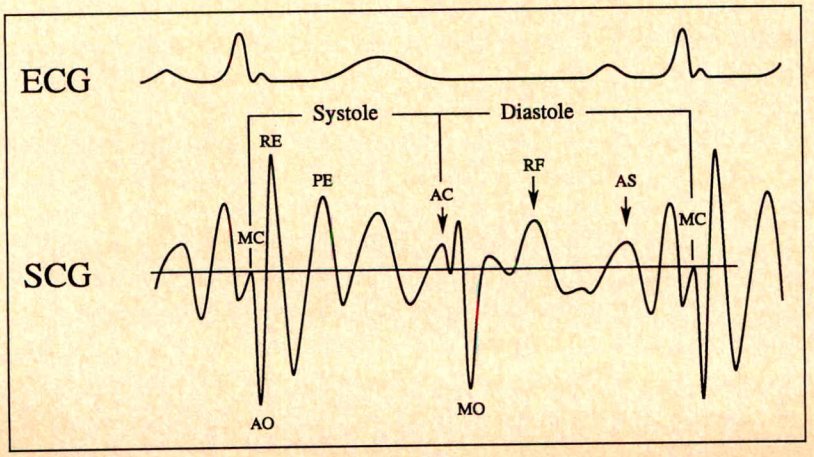


FIGURE 1. Simultaneous electrocardiogram (ECG) and seismocardiogram (SCG) are shown. SCG waves are labeled based on studies using simultaneous pulsed Doppler and M-mode echocardiography. AC = aortic valve closure; AO = aortic valve opening; AS = peak velocity of transmitral flow due to atrial systole; MC = mitral valve closure; MO = mitral valve opening; PE = peak velocity of flow in left ventricular outflow tract; RE = onset of rapid ejection in the left ventricular outflow tract; RF = peak velocity of transmitral flow in early diastole.

raphy using 2 readers, the interobserver agreement was 80% (n = 108) and the intraobserver agreement was 88% (n = 50).

Electrocardiography: Each angioplasty patient had 6- to 9-lead electrocardiograms recorded at the same time as the seismocardiograms. These recordings always included leads I, II, III, aVL, aVF and V_6, and usually included V_4 and V_5. These recordings were arranged in sets for comparison without knowledge of the baseline electrocardiogram, in the same manner as for the seismocardiograms. Each electrocardiogram was scored for change from baseline: 0 = no change, 1 = 0.5 mm ST depression, 2 = ≥1.0 mm ST depression, and 3 = ≥0.5 mm ST elevation.

Data analysis: The mean seismocardiographic and electrocardiographic scores for change from baseline were calculated for each time interval. The following angioplasty time intervals were compared with volunteer data: second angioplasty baseline versus volunteer 1 hour recording, balloon across lesion before inflation versus 1 day, 60 second inflation versus 1 week, 60-second deflation versus 1 month, and final postangioplasty recording versus 3-month recording. These were compared by unpaired *t* test. Also, the changes from baseline at each interval were compared by paired *t* test. The highest score of each patient and volunteer was tabulated. These highest scores were compared by unpaired *t* test. The percentage of patients with scores of either 2 or 3 was tabulated for each time period. The data for patients undergoing angioplasty of each of the 3 coronary arteries were tabulated separately and compared. The seismocardiographic and electrocardiographic data were not compared, because patients did not have 12-lead recordings in this study.

RESULTS

Patient characteristics: Recordings were made from 35 angioplasty patients and 15 normal volunteers; adequate seismocardiograms were obtained from all. Examples of seismocardiographic recordings obtained from a patient undergoing angioplasty of the right coronary artery and a normal volunteer are shown in Figures 2 and 3. The patients undergoing angioplasty included 16 left anterior descending coronary artery dilatations, 11 right coronary artery dilatations and 8 circumflex artery dilatations. (No patient had 2 different arteries dilated during the same procedure.) The mean age ± standard deviation was 63 ± 10 years for patients and 28 ± 5 years for volunteers. The reason for angioplasty was stable angina in 13 patients, unstable angina in 9 patients and recent myocardial infarction in 13 patients. Based on left ventriculography or 2-dimensional echocardiography, 2 had dyskinetic, 3 had akinetic, 7 had hypokinetic and 21 had normal segments before angioplasty in the perfusion zone of the artery being dilated (2 were unknown). Collateral flow to the perfusion zone of the dilated artery was seen before angioplasty in 11 patients, whereas 22 patients had no collateral flow and 2 were unknown. Overall, 18 patients did not have either preangioplasty akinesia, dyskinesia, or collateral flow that might reduce the likelihood of inducing ischemic wall motion abnormality during balloon inflation.

Angioplasty patients versus volunteers: The mean seismocardiographic and electrocardiographic scores at each time period are shown in Figure 4. Although there was no difference in seismocardiographic scores between the 2 groups at baseline, at all other time periods the angioplasty patients had higher mean systolic and

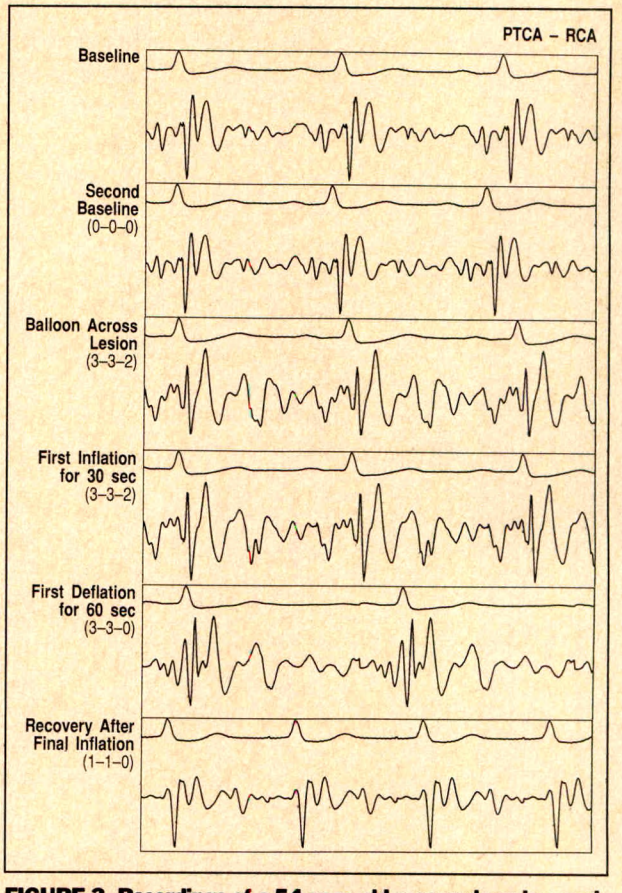


FIGURE 2. Recordings of a 54-year-old man undergoing angioplasty of a right coronary artery lesion at the times indicated. The patient had stable angina, normal left ventricular function, and 1-vessel disease of the right coronary (RCA) with no evidence for collateral flow from the left coronary. He did have chest pain during the balloon inflation. The seismocardiograms are arranged vertically and aligned to the baseline electrocardiogram for wave comparison. Each *line* represents 1 signal-averaged cardiac cycle. The scores for change from baseline are shown for each recording in the following order: systolic seismocardiographic, diastolic seismocardiographic, electrocardiographic score. PTCA = percutaneous transluminal coronary angiography.

TABLE I Percentage of All Angioplasty Patients with Moderate or Marked Change from Baseline

Time of Recording	Second Baseline (n = 35)	Balloon Across Narrowing (n = 15)	First Inflation (seconds)		First Deflation (seconds)		After Final Inflation (n = 34)
			30 (n = 32)	60 (n = 31)	60 (n = 31)	120 (n = 13)	
Systolic SCG	11	67	75	71	74	62	71
Diastolic SCG	14	53	59	61	61	77	47
Electrocardiography	0	23	44	42	23	22	0

Data expressed as percentage of patients at each time point with change from baseline that was either moderate (score = 2) or marked (score = 3).
SCG = seismocardiogram.

diastolic scores than the volunteers. The electrocardiogram did not change at baseline but did change significantly as soon as the balloon was placed across the lesion. Although the electrocardiogram returned to baseline at the final recording after angioplasty, the seismocardiogram had not yet returned to baseline.

The percentage of patients and volunteers with seismocardiographic scores (and patients with electrocardiographic scores) of 2 or 3 is listed in Tables I and II. Most seismocardiographic and more than half of all electrocardiographic scores were already moderately to markedly changed (score 2 or 3) when the balloon was placed across the lesion, before inflation. Up to 75% of patients had systolic and 61% had diastolic seismocardiographic changes during angioplasty, whereas the volunteers had minimal seismocardiographic changes.

Seismocardiography scores for each coronary artery: For each coronary artery, the percentage of patients developing moderate to marked seismocardiographic changes (score 2 or 3) from baseline is listed in Table III. Changes were seen most frequently during angioplasty of the left anterior descending artery, during which 87% of patients showed systolic scores of ≥ 2.

The mean maximal seismocardiographic scores are shown in Figure 5. For all angioplasty patients, the mean maximal systolic score was 2.5 ± 0.8 and diastolic score was 2.3 ± 0.8, compared with scores in volunteers, who had a mean maximal systolic score of 1.0 ± 0.9 and diastolic score of 0.7 ± 0.9 ($p < 0.001$ for both comparisons). The systolic and diastolic scores

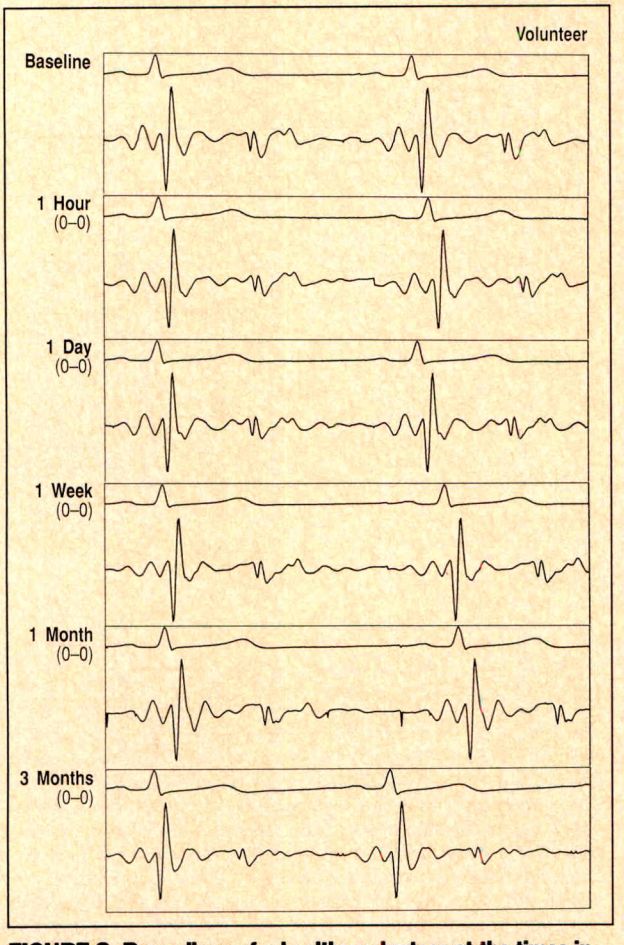


FIGURE 3. Recordings of a healthy volunteer at the times indicated. Recordings are aligned as in Figure 2 and represent 1 signal-averaged cardiac cycle. The scores for change from baseline are shown for each recording in the following order: systolic and diastolic seismocardiographic scores.

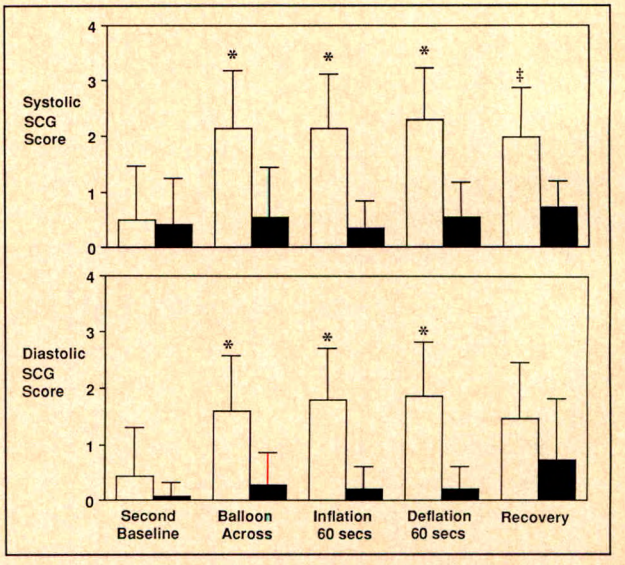


FIGURE 4. The mean systolic and diastolic seismocardiographic (SCG) scores for patients *(open bars)* and volunteers *(solid bars)* are shown at each time period. *p <0.0001; ‡p <0.001 for patients versus volunteers.

were, respectively: 2.7 ± 0.7 and 2.5 ± 0.7 for the left anterior descending artery; 2.4 ± 0.9 and 2.0 ± 0.9 for the right coronary coronary; and 2.3 ± 0.7 and 2.1 ± 0.8 for the circumflex artery ($p < 0.01$ for each vs the volunteers).

Effect of baseline variables on seismocardiography: We compared the seismocardiographic scores of the 18 patients with no collateral flow and either normal or hypokinetic wall motion in the area perfused by the artery being dilated (the group most likely to show an effect during angioplasty) with the 17 patients with either collateral flow or akinetic/dyskinetic wall motion: their maximal systolic scores were 2.8 ± 0.5 and 2.2 ± 0.9 ($p < 0.01$), respectively, and their maximal diastolic scores were 2.4 ± 0.9 and 2.0 ± 0.8 ($p = 0.06$), respectively.

We also compared patients who had a normal baseline seismocardiographic wave morphology (21 patients) with those who had an abnormal baseline recording (14 patients) to evaluate the likelihood of recovery to baseline. Their recovery systolic scores were 1.8 ± 0.9 and 2.2 ± 0.9 ($p = 0.07$), respectively, and diastolic scores were 1.3 ± 1.1 and 1.7 ± 0.8 ($p = 0.16$), respectively .

TABLE II Percentage of Volunteers with Moderate or Marked Change from Baseline

	Days				
Time from Baseline	1/24* (n = 15)	1 (n = 15)	7 (n = 15)	30 (n = 15)	90 (n = 7)
Systolic SCG	7	13	0	7	0
Diastolic SCG	0	7	0	0	14

*1 hour/24 hours a day.
Data expressed as percentage of patients at each time point with change from baseline that was either moderate (score = 2) or marked (score = 3).
SCG = seismocardiogram.

DISCUSSION

In this blinded comparison study, the seismocardiogram usually showed changes during balloon coronary angioplasty, whereas similar changes were not seen in the control group of normal volunteers over a 3-month period. The seismocardiographic changes were seen during dilation of all 3 of the major epicardial coronary arteries. The seismocardiographic and electrocardiographic changes usually developed as soon as the balloon catheter was placed across the lesion, even before balloon inflation. Patients without collateral flow or akinetic/dyskinetic walls in the area undergoing an-

TABLE III Percentage of Angioplasties of Each Coronary Artery with Moderate or Marked Change from Baseline

Time of Recording	Second Baseline (n = 35)	Balloon Across Lesion (n = 15)	First Inflation (seconds)		First Deflation (seconds)		After Final Inflation (n = 34)
			30 (n = 32)	60 (n = 31)	60 (n = 31)	120 (n = 13)	
Systolic Seismocardiogram							
LAD	13	80	87	86	77	67	73
Right	0	50	64	40	64	50	64
LC	25	75	67	86	86	—	75
Diastolic Seismocardiogram							
LAD	19	60	73	71	62	83	60
Right	9	50	45	40	55	67	36
LC	13	50	50	71	71	—	38

Data expressed as percentage of patients at each time point with change from baseline that was moderate (score = 2) or marked (score = 3).
LAD = left anterior descending (n = 16); LC = left circumflex (n = 8); Right = right coronary artery (n = 11).

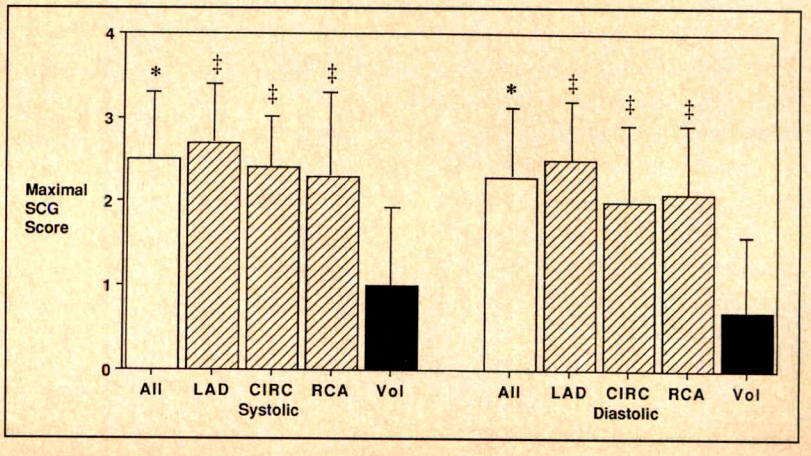


FIGURE 5. The mean maximal systolic and diastolic seismocardiographic (SCG) scores at any time period are shown for patients and volunteers (Vol). CIRC = circumflex artery; LAD =left anterior descending artery; RCA = right coronary artery. *p <0.0001; ‡p <0.01 for patients versus volunteers.

gioplasty showed greater seismocardiographic changes during the procedure. The seismocardiographic changes persisted at least several minutes after the final inflation, at a time when the electrocardiogram had returned to baseline.

Comparison with previous work: Anterograde coronary blood flow is usually completely obstructed during inflation of the angioplasty balloon catheter, although collateral flow may provide flow to the distal vessel in some cases.[14] During balloon inflation, a wall motion abnormality consistently develops in the distribution of the artery undergoing dilatation, as confirmed by 2-dimensional echocardiography and digital subtraction angiography.[10–12] Electrocardiographic and hemodynamic changes are observed during this same period of time.[8–12,15] All of these changes return to normal by the end of the procedure.[9–12,15] Our observation of incomplete return of the seismocardiogram to its baseline appearance is unexplained, but may suggest that the myocardium remains mildly abnormal for more than a few minutes after angioplasty in some patients. Alternatively, although asymptomatic on arrival in the angioplasty laboratory, some of the patients might have had left ventricular ischemia that was already affecting the baseline seismocardiogram. One study of transmitral velocity, measured by Doppler, demonstrated that patients had asymptomatic baseline abnormalities just before angioplasty.[13] We did note that patients who had normal baseline seismocardiograms were more likely to show return to baseline appearance during recovery than the patients with abnormal baseline recordings.

The seismocardiogram is related to other forms of displacement cardiography that measure movement of the body in response to cardiac motion. Apexcardiography uses a pressure transducer placed over the apex of the heart. Although limited by the sensitivity of the detector and motion artifact at the apex, changes in the apexcardiogram have been observed in coronary artery disease.[2] Kinetocardiography is a technique that uses a cylinder placed over the sternum to detect movement of the air column within the cylinder by a pressure transducer placed on top of the cylinder.[3] This technique is limited by low sensitivity and complex apparatus. Ballistocardiography is a technique that was extensively studied a number of years ago, in which an accelerometer was used to detect motion of a platform in response to movements of the entire body from cardiac activity. Changes in the ballistocardiogram were also observed in patients with coronary artery disease.[4,5] Cardiokymography is a technique that uses a capacitor to induce an electromagnetic field that penetrates the chest wall near the apex; the device detects distortion of the field due to cardiac movement. Exercise cardiokymography has been reported to be effective for detecting coronary artery disease, but its use is technically demanding.[6,7] Seismocardiography overcomes many of the limitations of other forms of displacement cardiography in that it is highly sensitive, rapid, very reproducible, minimally affected by motion artifact in the supine position, and reliably obtained from most if not all patients.

Study limitations: Although seismocardiography consistently showed changes during obstruction of coronary blood flow in this study, it is not known whether the seismocardiogram will show similar changes during acute myocardial infarction. Although it is likely that changes in the seismocardiographic waves are due to changes in left ventricular wall motion induced by ischemia, this study did not directly evaluate this point. Since the seismocardiogram did not completely return to its baseline appearance 5 minutes after the final balloon inflation, further study of the time course of its recovery is needed. Also, we did not obtain 12-lead electrocardiograms during this study, so that the sensitivity of electrocardiography and seismocardiography cannot be compared. Finally, we did not use quantitative seismocardiography. Application of quantitative techniques for measurement of the seismocardiographic waves may be useful.

Implications: Seismocardiography may be a useful clinical tool for detecting myocardial ischemia during or after percutaneous transluminal coronary angioplasty. Whereas electrocardiography is a useful technique for monitoring early closure after dilatation of a coronary artery, additional noninvasive monitoring techniques could be helpful. It is possible that seismocardiography may be useful during other clinical syndromes associated with closure of a coronary artery such as documented acute myocardial infarction, particularly when attempts are being made to restore coronary blood flow with thrombolytic therapy or other interventions. Seismocardiography may be a useful tool to enhance the diagnostic accuracy of the electrocardiogram for the evaluation of chest pain of suspected myocardial infarction. Furthermore, seismocardiography may enhance the diagnostic accuracy of provocative maneuvers to induce myocardial ischemia, such as exercise testing and dobutamine stress testing. In our preliminary studies, exercise seismocardiography enhanced the diagnostic accuracy of exercise electrocardiography.[16,17]

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Epicardial Mapping in Patients with "Nodoventricular" Accessory Pathways

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Some patients with electrophysiologic features suggesting nodoventricular fibers have been shown to have right parietal atrioventricular (AV) accessory pathways with decremental conduction properties intraoperatively. The experience with 11 patients (7 women and 4 men, mean age ± standard deviation 25 ± 5 years) who had electrophysiologic features consistent with a nodoventricular pathway and who underwent operative correction was reviewed. At electrophysiologic study, all patients had absent or minimal preexcitation in sinus rhythm. During atrial pacing and extrastimulus testing, maximal preexcitation with left bundle branch block morphology developed and the AH and AV intervals progressively prolonged. Preexcited tachycardia was initiated in all patients (AV reentrant tachycardia in 10 patients and AV node reentrant tachycardia in 1 patient).

At operation all patients had a right parietal accessory pathway demonstrated. Intraoperative mapping demonstrated the earliest site of ventricular activation during anterograde preexcitation to be at the midanterior right ventricle, consistent with insertion of these pathways into the right bundle branch system, in 7 patients. The ventricular insertion was at the AV groove in 4 patients, in keeping with the typical Wolff-Parkinson-White syndrome. Retrograde conduction over the pathway was not demonstrated in any patient. Two patients had evidence of a second accessory AV pathway in the left paraseptal region.

Operative AV node ablation was electively performed in 2 patients without affecting preexcitation in either case. In 1 of these patients, accessory pathway conduction was temporarily abolished by ice mapping in the right anterolateral AV groove. In the remaining 9 patients the accessory pathway was permanently ablated in the right anterolateral AV groove. Three patients underwent operative dissection of the AV node as a concomitant procedure to prevent AV node reentrant tachycardia.

All patients in this study with an electrophysiologic presentation suggesting a nodoventricular pathway were found to have a right AV pathway with decremental properties mimicking a nodoventricular pathway. Epicardial activation during anterograde preexcitation suggested ventricular insertion at the base of the heart as for typical AV pathways or insertion in the right bundle branch system.

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Rate-dependent prolongation of atrioventricular (AV) conduction in the presence of overt preexcitation has been postulated to result from an abnormal nodoventricular connection.[1–9] Such a connection was first anatomically described by Mahaim and Winston in 1941.[1] Patients suspected of having nodoventricular connections typically have a normal or minimally preexcited electrocardiogram with a left bundle branch block pattern during sinus rhythm. At electrophysiologic study, marked preexcitation with a left bundle branch block pattern develops during right atrial incremental pacing and the AH and AV intervals progressively prolong as the His-delta wave interval shortens. An alternate explanation for these findings is the presence of a right-sided accessory pathway with decremental conduction properties, as was the case in 2 patients previously described.[10] The following report describes the operative findings in all patients with electrophysiologic features suggesting a nodoventricular connection treated at this institution.

METHODS

Patients with a preoperative diagnosis of a nodoventricular pathway who underwent surgery at this institu-

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tion between 1983 and January 1990 were included in this study. The following electrophysiologic findings were found in all patients and were considered consistent with the presence of a nodoventricular connection: (1) absent to minimal preexcitation in sinus rhythm with left bundle branch block morphology during maximal preexcitation exposed by atrial pacing; (2) more marked preexcitation with right atrial pacing versus left atrial pacing at comparable cycle lengths; and (3) both the AH and A to delta intervals progressively prolonged with increasing prematurity of extrastimuli or more rapid rate ("decremental accessory pathway conduction") during atrial extrastimulus testing or incremental pacing.

Electrophysiologic study procedure: The method of study has been described in detail elsewhere.[11] Briefly, patients had multipolar electrode catheters positioned under local anesthetic at the high right atrium, right ventricular apex, His bundle recording position and the coronary sinus. The coronary sinus catheter consisted of a quadripolar catheter with 1-cm interelectrode spacing. Unipolar electrograms were obtained from each of the poles of the coronary sinus catheter and filtered from 0.05 to 400 Hz. Bipolar electrograms were also obtained from paired coronary sinus, right atrial, right ventricle and His catheter electrodes and filtered at 40 to 400 Hz. Stimulation consisted of right atrial and right ventricular extrastimulus testing and incremental pacing. Recordings were made on a Siemens 16 channel mingograph chart recorder at a paper speed of 100 mm/s.

Intraoperative mapping: Intraoperative mapping was performed during sinus rhythm, atrial and ventricular pacing and during reentrant tachycardia. The earliest site of atrial activation during ventricular pacing or reentrant tachycardia was localized using a handheld probe scanning 17 predetermined atrial sites adjacent to the AV ring. Ice-mapping of the AV ring using a 0.5-cm diameter cryoprobe cooled to 0°C was used in 6 patients. The site in the AV ring where anterograde preexcitation was abolished by cooling or by dissection was considered to be the atrial insertion of the accessory pathway. Epicardial ventricular mapping was performed using either a roving electrode probe (5 patients) or a computerized mapping system (Biomedical Instruments Incorporated, Cardiac Mapping System, Toronto, Ontario, Canada) with an epicardial sock array of 56 bipolar electrode pairs (6 patients).

Operative procedure: The surgical technique for operative correction for Wolff-Parkinson-White syndrome and for AV nodal tachycardia used at this center has been described.[12,13] In the first 2 patients, initial attempts at nodoventricular fiber ablation consisted of perinodal dissection followed by AV node ablation. Later patients underwent a direct primary approach to the accessory pathway in the right AV ring using map-guided epicardial or endocardial dissection with additional cryotherapy. In patients with associated AV nodal reentrant tachycardia, AV node modification[13] was performed after ablation of the accessory pathway. This report includes the 2 patients reported previously.[10]

TABLE I Clinical and Electrophysiologic Features in the 11 Study Patients

Pt. No.	Age (yr.)	Clinical Preexcited Tachycardia (cycle length)	AF	Preexcitation Axis	AVNRT	SRR	AP ERP
1	26	0 (300)*	0	−45°	+	275	260
2	29	+ (360)	0	−60°	0	—	—
3	17	+ (250)	0	−30°	+	280	270
4	26	+ (360)	0	−45°	0	250	<240
5	24	+ (350)	0	45°	+	—	260
6	31	+ (200)	0	−45°	+	220	—
7	25	+ (300)	+	−45°	0	220	<250
8	27	+ (270)	+	−45°	0	240	290
9	14	+ (280)	0	0°	0	250	280
10	27	+ (290)	0	−60°	0	250	<290
11	27	0 (320)*	+	−45°	0	220	—

*Preexcited tachycardia was inducible at electrophysiologic study but not documented clinically.
AF = atrial fibrillation; AP ERP = accessory pathway effective refractory period at drive cycle length of 600 ms; AVNRT = atrioventricular node reentrant tachycardia; SRR = shortest preexcited interval in atrial fibrillation; + = yes; 0 = no; — = not available.

RESULTS

Clinical characteristics: The clinical and electrophysiologic characteristics of the 11 patients are listed in Table I. There were 6 women and 5 men (mean age ± standard deviation 25 ± 5 years [range 14 to 31]). Symptoms had been present from 5 to 15 years (mean 10 ± 5). All patients had no or minimal preexcitation during sinus rhythm, typical decremental anterograde conduction over the accessory pathway and preexcitation with a left bundle branch block morphology, more marked during right atrial pacing than pacing at comparable cycle lengths from the coronary sinus (Figure 1). The mean anterograde effective refractory period of the accessory pathway was 268 ± 18 ms and the shortest RR interval between 2 preexcited QRS complexes during atrial fibrillation was 245 ± 23 ms. Nine patients had a central pattern of retrograde conduction with decremental properties consistent with conduction in retrograde manner over the AV node. Two patients had the shortest ventriculoatrial interval during reentrant tachycardia and ventricular pacing recorded in the proximal coronary sinus. Retrograde conduction in these patients was rate-independent and considered to be over a left paraseptal accessory pathway.

Arrhythmias: Preexcited reciprocating tachycardia could be initiated in all patients. The mechanism of this tachycardia (Figure 2) was considered to be AV reentrant tachycardia utilizing the right accessory pathway as the anterograde limb and the normal ventriculoatrial

conducting system as the retrograde limb in 8 patients. In these patients, retrograde atrial activation pattern was central, and right ventricular extrastimuli delivered during tachycardia preexcited the atrium at long coupling intervals, suggesting a macroreentrant circuit. In 2 patients, preexcited tachycardia was associated with earliest atrial activation in the proximal coronary sinus, consistent with the presence of a paraseptal accessory pathway participating as the retrograde limb of the tachycardia. In 1 of these patients transition between narrow complex and preexcited tachycardia without change in cycle length was observed (Figure 3). The right-sided accessory pathway was considered a bystander in the tachycardia. AV node reentrant tachycardia was initiated in 4 patients. In these patients the tachycardia was initiated only after a critical AH delay, retrograde atrial activation was earliest in the His bundle recording with a ventriculoatrial interval <60 ms, and ventricular extrastimuli delivered during tachycardia at a time when the His bundle was refractory failed to preexcite the atria. In 1 patient, this tachycardia was preexcited, the accessory pathway acting as a bystander. In no patient was there unequivocal evidence for a true nodoventricular fiber such as ventriculoatrial block during preexcited tachycardia.

Intraoperative mapping: Details of intraoperative mapping and surgery are listed in Table II. The earliest site of ventricular activation during maximal preexcitation occurred in the right ventricular anterior wall similar to sinus rhythm in 7 patients, and in the anterior wall of the right ventricle at the AV groove in 4 patients (Figures 4 and 5). An attempt at cooling the right bundle branch over the right ventricular myocardium in 3 patients did not abolish preexcitation. Ice-mapping of the right AV anulus from the epicardial surface abolished preexcitation after dissection in all 6 patients in whom this was done.

The earliest site of atrial activation during ventricular pacing or during tachycardia was central and consistent with conduction over the AV node in 9 patients. In 2 patients, earliest atrial activation occurred in the left paraseptal position. These latter patients were

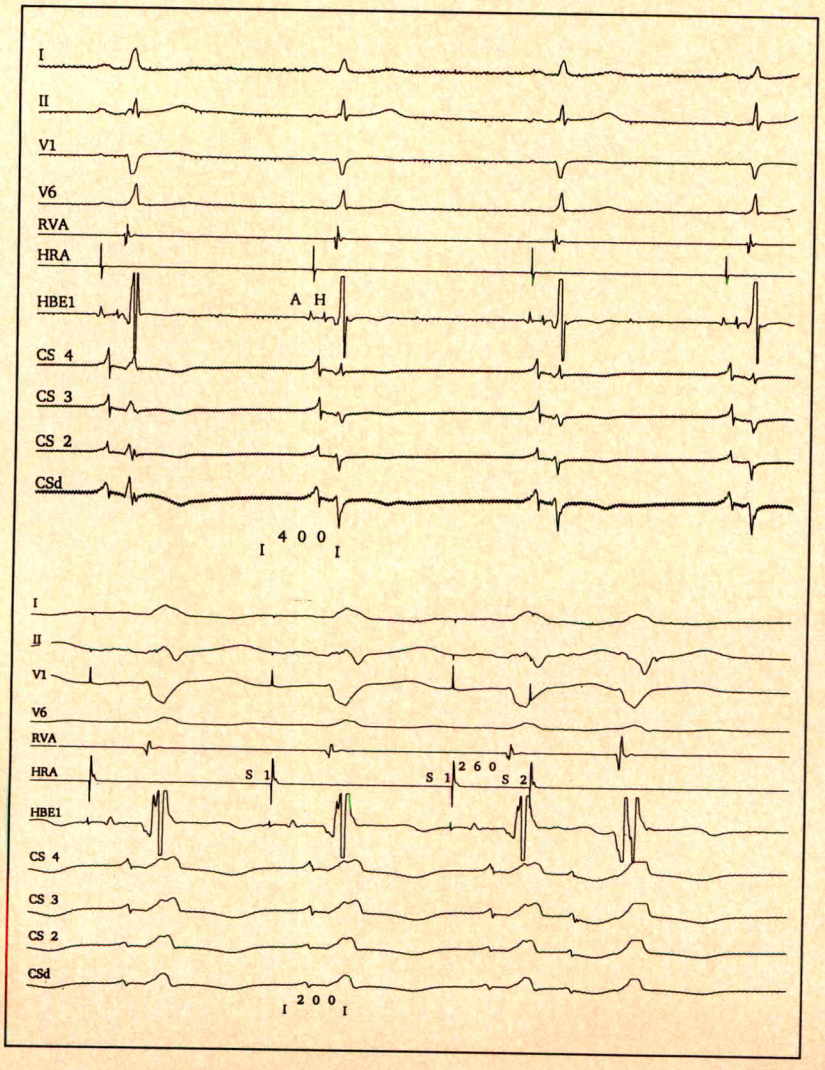


FIGURE 1. Electrophysiologic study recordings from a patient with a preoperative diagnosis of nodoventricular pathway. Intraoperatively, the patient was found to have a right parietal accessory atrioventricular pathway. *Top,* during sinus rhythm no preexcitation is evident. The AH interval is 85 ms and the HV interval is 45 ms. *Bottom,* atrial extrastimulus testing. At a basic drive of 600 ms (S1), an atrial extrastimulus (S2) is delivered with a coupling interval of 260 ms. All paced complexes are now preexcited with a left bundle branch block pattern. The A to delta-wave interval has prolonged visibly after the extrastimulus. Surface leads I, II, III, V_1 and V_6, and intracardiac electrograms from the right ventricular apex (RVA), high right atrium (HRA), His position (HBE1) and coronary sinus proximal to distal (CS 4-CSd) are displayed.

TABLE II Operative Procedure and Findings

Pt. No.	Earliest Ventricular Activation During Preexcited Tachycardia	Delta-Earliest Ventricular Activation (ms)	Second AP	Epicardial Dissection Site	Endocardial or Epicardial Loss of Preexcitation	AV Node Operation
1	Right anterior ventricle	−30				Ablation
2	Right anterior ventricle	−5		Right anterolateral AV sulcus (ice mapping)		Ablation
3	Right anterior ventricle	−10		Right anterolateral AV sulcus	Endocardial	Modification
4	Right anterolateral AV anulus	0		Right anterolateral AV sulcus	Endocardial	
5	Right anterior ventricle	5		Right anterolateral AV sulcus	Endocardial	Modification
6	Right anterolateral AV anulus	0		Right anterolateral AV sulcus	Endocardial	Modification
7	Right anterolateral AV anulus	−5	LPS (concealed)	Right anterolateral AV sulcus	Epicardial	
				Left posteroseptal AV sulcus		
8	Right anterior ventricle	−5	LPS (bidirectional)	Right anterolateral AV sulcus	Endocardial	
				Left posteroseptal AV sulcus		
9	Right anterior ventricle	−5		Right anterolateral AV sulcus	Endocardial	
10	Right anterior ventricle	−15		Right anterolateral AV sulcus	Epicardial	
11	Right anterolateral AV anulus	−30		Right anterolateral AV sulcus	Epicardial	

AP = accessory pathway; AV = atrioventricular; LPS = left posteroseptal.

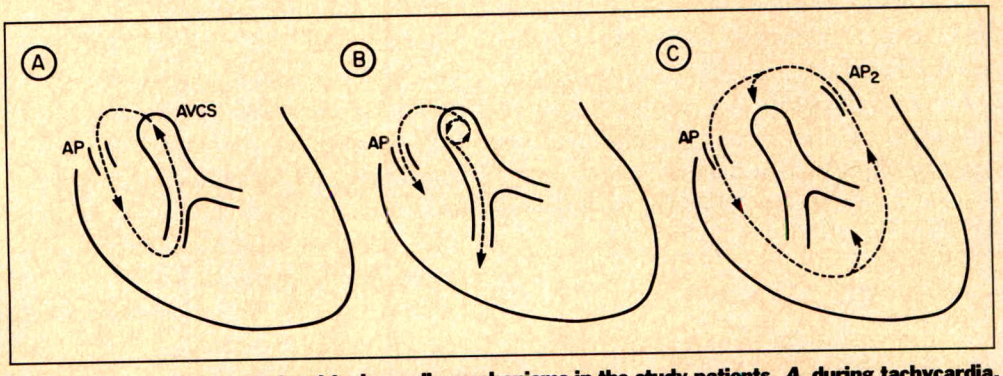


FIGURE 2. Schematic representation reentrant tachycardia mechanisms in the study patients. *A*, during tachycardia, anterograde conduction is over the right parietal accessory pathway (AP) and retrograde conduction over the atrioventricular conducting system (AVCS) (n = 8). *B*, atrioventricular node reentrant tachycardia (n = 4). Anterograde preexcitation is possible due to bystander participation of the AP, and was demonstrated in 1 patient. *C*, retrograde conduction during tachycardia is over a second AP (n = 2). Anterograde conduction may occur over the right parietal AP or the AVCS.

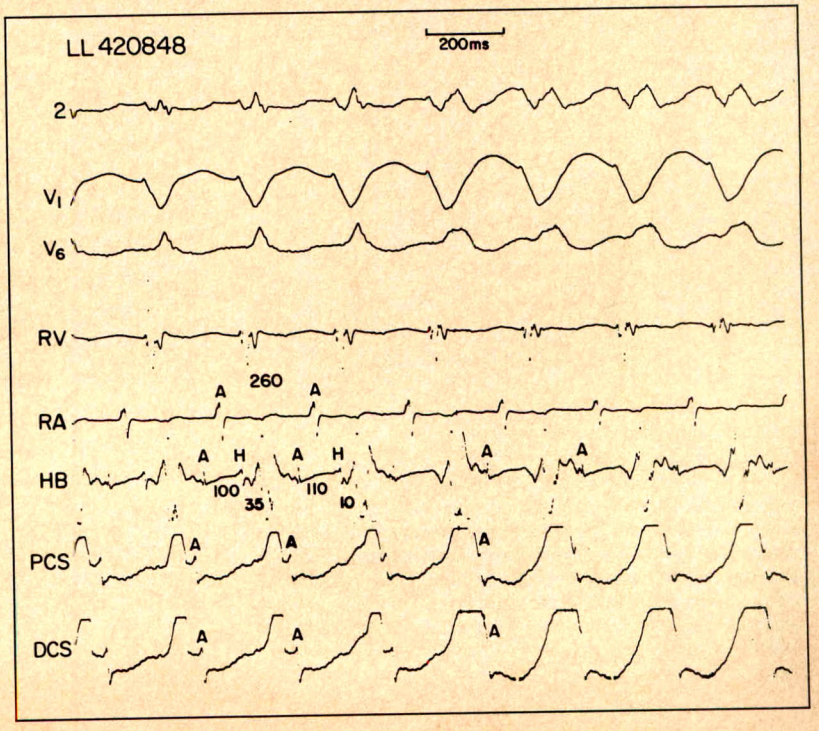


FIGURE 3. Electrophysiologic recordings during atrioventricular reentrant tachycardia. In this case, earliest retrograde atrial activation is occurring in the proximal coronary sinus recording due to conduction over a second accessory pathway (mechanism *C*, Figure 2). Anterograde conduction is occurring over both the atrioventricular node and the right parietal accessory pathway. Progressive fusion is seen as the HV interval shortens and preexcitation becomes more marked. Surface leads 2, V_1 and V_6, and intracardiac recordings from the right atrium (RA), right ventricle (RV), His position (HB), proximal coronary sinus (PCS) and distal coronary sinus (DCS) are displayed. A = atrial electrogram; H = His potential.

thought to have a second accessory pathway in the left paraseptal region. No patient had retrograde conduction over the right parietal accessory pathway.

Operative procedures: AV node ablation was performed electively as the initial surgical approach during our early experience with the first 2 patients. This was in response to the hypothesis prevailing at that time that these pathways were truly nodoventricular. This procedure did not affect preexcitation in either patient. Preexcitation was temporarily abolished in 1 of these patients by ice mapping in the right AV groove. In the next 9 patients, dissection of the right AV groove was performed with loss of preexcitation in all. An epicardial dissection was initially performed, which resulted in loss of preexcitation in 3 cases. In the remaining 6 patients, preexcitation was only abolished after endocardial dissection or cryoablation. Endocardial cryoablation through a purse string suture in the right atrium was also performed in the 3 patients in whom loss of preexcitation occurred during epicardial dissection. Three patients with AV node reentrant tachycardia underwent AV node modification after accessory pathway ablation. One patient with a second bidirectional accessory pathway (patient 8) underwent epicardial dissection of the posteroseptal pathway before the "nodoventricular" pathway was mapped and ablated. The patient with a second unidirectional accessory pathway (patient 7) had that pathway ablated with an epicardial approach after the "nodoventricular pathway" had been ablated.

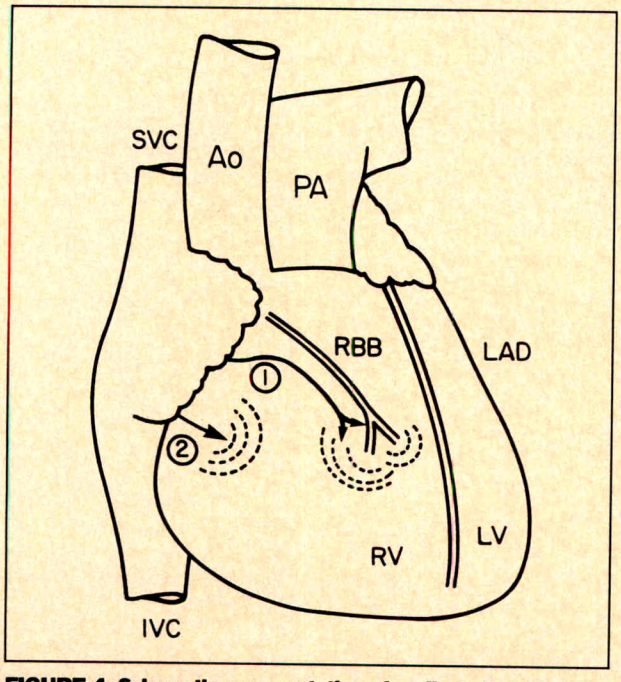


FIGURE 4. Schematic representation of earliest site of anterograde ventricular activation during maximal preexcitation. Site "1" is at the midanterior right ventricle and corresponds to a right bundle branch system insertion and site "2" represents direct insertion into the ventricular myocardium at the atrioventricular groove. Seven patients had earliest ventricular activation at site 1 and 4 patients at site 2. Ao = aorta; IVC = inferior vena cava; LAD = left anterior descending coronary artery; LV = left ventricle; PA = pulmonary artery; RBB = right bundle branch; RV = right ventricle; SVC = superior vena cava.

DISCUSSION

To explain the unusual features of rate-dependent prolongation of AV conduction in the presence of overt preexcitation, the existence of an abnormal nodoventricular connection has been postulated.[1-9] The left bundle branch block pattern of preexcitation suggests a right ventricular or right bundle branch insertion site. Such a connection may form 1 limb of a reentrant circuit with the normal AV conducting system forming the other limb, in addition to other potential tachycardia mechanisms. Mahaim fibers may potentially provide this anatomic substrate and explain these electrophysiologic findings. An alternative explanation for these findings would be an AV connection with decremental conduction properties. In this study, all patients with preoperative characteristics of a nodoventricular connection were found to have a right parietal AV connection. Thus, it is likely that the electrophysiologic features previously described uncommonly indicate the presence of a nodoventricular connection, but more typically are due to a right-sided accessory pathway with decremental conduction, giving rise to a "pseudo-nodoventricular" electrophysiologic pattern.

These findings are consistent with previous reports of patients with a diagnosis of nodoventricular connection.[14,15] Although Gallagher et al[3] attributed these features to the presence of a nodoventricular pathway, he recognized the alternative explanation of an AV pathway with decremental conduction. Gillette et al[14] described the operative findings in 4 patients with features suggestive of a nodoventricular connection who were found to have a right-sided accessory pathway. Similarly, Ross et al[15] found that these features were due to an accessory pathway with decremental conduction in 3 reported cases. This study expands on these reports in this relatively rare patient group and provides new observations on the ventricular insertion site of the accessory pathway. We and others[10] initially observed earliest ventricular activation during maximal preexcitation at the anterior right ventricle in a pattern similar to epicardial breakthrough by way of the Purkinje or right bundle branch system. Subsequently, we also observed epicardial breakthrough at the base of the heart identical to typical AV pathways. A similar pattern of epicardial breakthrough was described in 1 previously reported case.[14] Consequently, these pathways may have 1 of ≥2 patterns of ventricular insertion, 1 into

the ventricular myocardium at the AV anulus and 1 probably directly into the right bundle branch system (Figure 4). Theoretically, the site of ventricular insertion might be identified during the electrophysiologic study by analysis of the VH intervals during preexcited tachycardia. Because the His potential was not consistently recorded during tachycardia in our patients, it was not possible to confirm this hypothesis.

All patients in this study had inducible preexcited tachycardia. The mechanism of this tachycardia was either preexcited AV reentrant tachycardia using the accessory pathway as the anterograde limb and the AV node or second accessory pathway as the retrograde limb, or AV node reentrant tachycardia with bystander participation of the pathway. Retrograde conduction over the right parietal pathway was always absent. Thus orthodromic reentrant tachycardia is unlikely to occur unless a second accessory pathway which conducts in the retrograde manner is present. Four of the 11 patients in this study had AV node reentry.

The clinical implications of these findings relate to therapy selection. Maneuvers aimed at interrupting the normal AV conducting system such as His bundle ablation are unlikely to result in loss of preexcitation, and indeed this has been the reported experience.[16,17] On the other hand, operative or catheter ablative techniques directed at an AV pathway should be successful in most patients with little threat to AV nodal conduction due to the right parietal location of these pathways. Successful catheter ablation of "nodoventricular fibers" at the right AV anulus has recently been reported[18] supporting these operative findings.

Although no patient in this series had a true nodoventricular pathway, this does not disprove the exis-

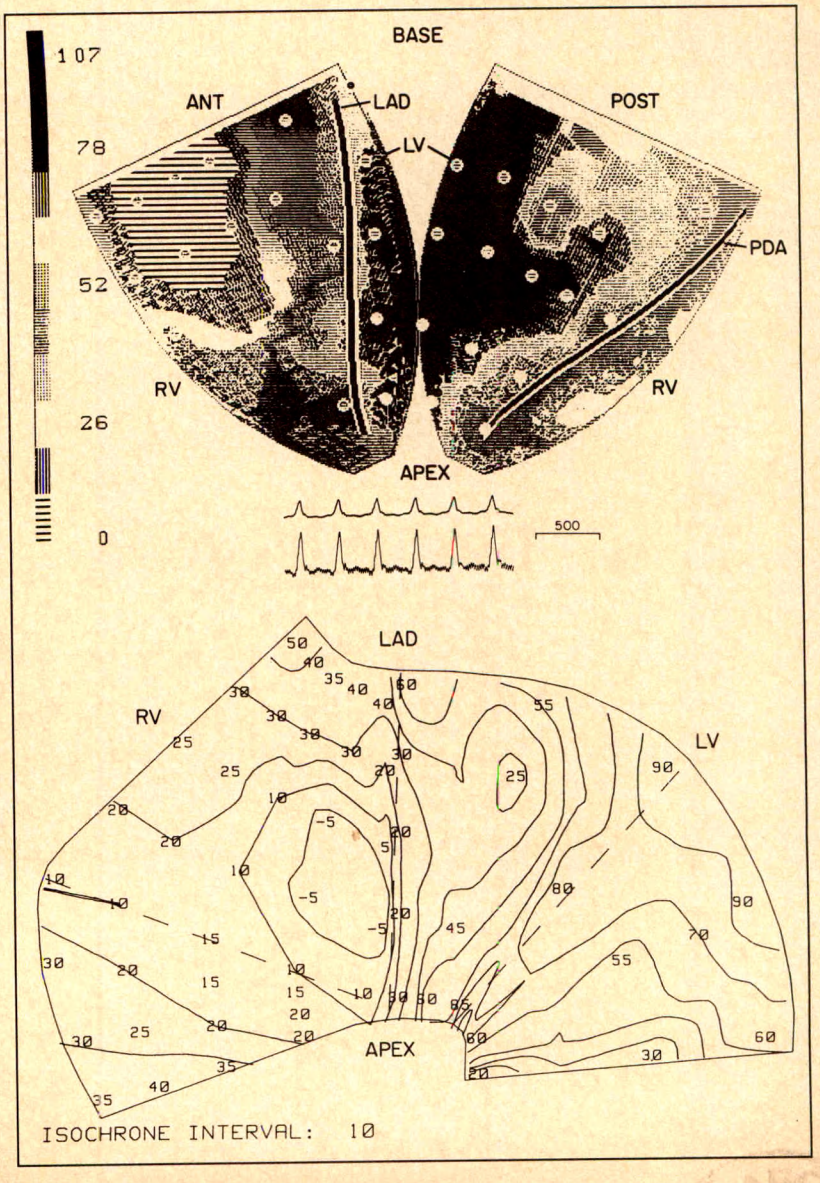


FIGURE 5. ***Top,*** **epicardial map from a patient using the computerized mapping system and epicardial sock electrodes obtained during preexcited tachycardia.** ***Cross-hatched area*** **represents the site of earliest ventricular activation. The location corresponds to the ventricular myocardium adjacent to the right atrioventricular groove (site 2, Figure 4,** ***bottom)*** **and demonstrates a right parietal accessory pathway. The** ***variously shaded verticle bar*** **indicates ventricular activation time in milliseconds relative to the onset of QRS on the surface electrocardiogram.** ***Bottom,*** **epicardial isochrone map during maximal preexcitation obtained using the roving hand-probe. In this case earliest epicardial activation is at the midanterior right ventricle, consistent with a distal insertion into the right bundle branch system (Figure 4,** ***top).*** **Numbers are ventricular activation times in milliseconds relative to the onset of the QRS. ANT = anterior; LAD = left anterior descending coronary artery; LV = left ventricle; PDA = posterior descending coronary artery; POST = posterior; RV = right ventricle.**

tence of these pathways. Good evidence has been presented for true nodoventricular pathways in several previous reports.[4,19] Our experience suggests that these pathways are exceedingly rare, and to date we have not yet demonstrated such a pathway at surgery.

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Time-Motion Reconstruction of Mitral Leaflet Motion from Two-Dimensional Echocardiography in Mitral Valve Prolapse

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To assess the contributions of mitral leaflet billowing and exaggerated systolic mitral anular expansion to posterior motion of mitral leaflets recognized as mitral valve prolapse (MVP) by M-mode echocardiography, time-motion reconstructions of the anteroposterior displacement of points equally spaced along the anterior and posterior mitral leaflets were derived by computer-assisted analysis of 2-dimensional echocardiograms. Late or holosystolic posterior displacement of mitral leaflets, ≥2 mm, occurred in the reconstructions from 24 of 24 (100%) patients with MVP with leaflet billowing and in 20 of 24 (83%) patients with MVP without leaflet billowing compared with 4 of 35 (11%) age-sex matched normal adults (both p <0.0000002). Posterior motion of the posterior mitral leaflet in time-motion reconstruction was significantly less with respect to the posterior end of the mitral anulus than with respect to the chest wall in patients with nonbillowing MVP (1.6 ± 1.9 vs 2.7 ± 1.6, p <0.02), but not in those with leaflet billowing (3.6 ± 1.8 vs 3.9 ± 1.8, p = not significant), because anular expansion contributed importantly to MVP in the former but not in the latter group. Thus, M-mode echocardiographic patterns of MVP reflect the separate but interacting effects of distinct abnormalities of mitral anular and leaflet dynamics.

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Both functional and structural abnormalities of the mitral valve are well documented in patients with primary mitral valve prolapse (MVP), including billowing of valve leaflets superiorly into the left atrium in systole[1–4] and anatomic redundancy of mitral leaflets, chordae and anulus.[5,6] Posterior motion of mitral leaflets detected by time-motion (M-mode) echocardiography may be associated either with mitral leaflet billowing or with exaggerated systolic expansion of the mitral anulus in the absence of leaflet billowing.[7] To determine whether systolic posterior displacement of mitral leaflet interfaces on M-mode echocardiograms could represent either leaflet billowing into the left atrium or leaflet displacement due to dynamic expansion of the mitral anulus, analyses were undertaken using computer reconstruction of time-motion tracings from 2-dimensional mitral valve images.

METHODS

Subjects: One hundred thirty-six subjects were randomly selected from the population enrolled in a previously described study of MVP.[8,9] As previously reported,[7] 83 subjects (61%) had a 2-dimensional echogram of the mitral valve of superior technical quality suitable for quantitative analyses. The control group included 35 subjects (23 women and 12 men; mean age 37 years [range 17 to 65]) who had no evidence of MVP or other cardiovascular diseases on echocardiographic and clinical examination, including auscultation in multiple positions and during isometric handgrip exercise. In the 48 study patients (32 women and 16 men; mean age 34 years [range 16 to 65]), a clinical diagnosis of MVP was made by standard M-mode echocardiographic criteria (described later), supported in most instances by the presence of typical auscultatory findings; no other mitral valve abnormality or cardiovascular condition was detected in these patients. No difference existed in age or sex distribution between the 2 groups. Thirty-two patients with MVP (67%) exhibited midsystolic click(s) (p <0.0001 vs controls), followed in 14 patients by a late systolic murmur (29%, p <0.001 vs controls); late or holosystolic murmurs were present in 24 patients with MVP (50%, p <0.0001 vs control subjects).

Echocardiographic recording: Echocardiograms were performed by an experienced research technician. Two-dimensional echocardiograms were recorded using a commercially available echocardiograph and a 3.5-MHz mechanical scanning transducer on ½-inch videotape; M-mode tracings made using the same transducer were recorded on black and white strip-chart paper at 50 mm/s. The accuracy of both horizontal and vertical calibrations was verified using an RMI phantom (Radiation Measurements, Inc., Middletown, Wisconsin). In selected patients with narrow intercostal spaces additional M-mode recordings were made with a smaller independent transducer (2.25 MHz, 13 mm diameter focused at 2 to 16 cm). Extensive recordings of the mitral valve were made from all available parasternal acoustic windows. M-mode tracings included multiple sweeps across the mitral valve from the left ventricle to the aorta along differently oriented paths as well as transverse scans of the valve, analogous to the T scan introduced for left ventricular measurements by Henry et al.[10]

Computerized analysis: Videotaped 2-dimensional echocardiograms were reviewed using a system that provided real-time and stop-frame viewing formats. Analyses reported here used the parasternal long-axis view because normal mitral valves may present an artifactual appearance of MVP in the apical 4-chamber view due to the saddle shape of the mitral anulus.[11] After repeated review of the study, a cardiac cycle was selected that allowed the best visualization of the anterior and posterior mitral leaflets from base to tip throughout the cardiac cycle. The entire systolic period (from the beginning of the R wave to the next opening of the mitral valve) of this cycle was examined frame by frame in stop-action format in long-axis view. In each frame, the mitral anular diameter was defined as extending between the hinge points at the base of each leaflet. The anterior and posterior leaflet positions in each frame were manually digitized using a graphic tablet. Tracings were made by an operator who had no knowledge of clinical or strip-chart M-mode findings.

A computer program was written in UCSD Pascal by one of the investigators (R.P.) for the quantitative analyses described later. The analysis program presented a sequential frame by frame graphic display of mitral valve motion. Furthermore, 10 points equally spaced along the length of each leaflet from its hinging point to free edge were automatically selected on each frame (Figure 1). Vertical (y-axis) distances from the transducer to each point were then computed and plotted against time (x-axis). A "time-motion" reconstruction similar to an M-mode study was thus obtained for each of the 10 points identified on each mitral leaflet. Reconstructions were also performed using the anterior end of the mitral anulus as an intracardiac reference point in order to examine mitral leaflet motion independently of overall heart motion, and using the posterior end of the mitral anulus as a reference point to examine the independence of mitral leaflet and anular motion patterns.

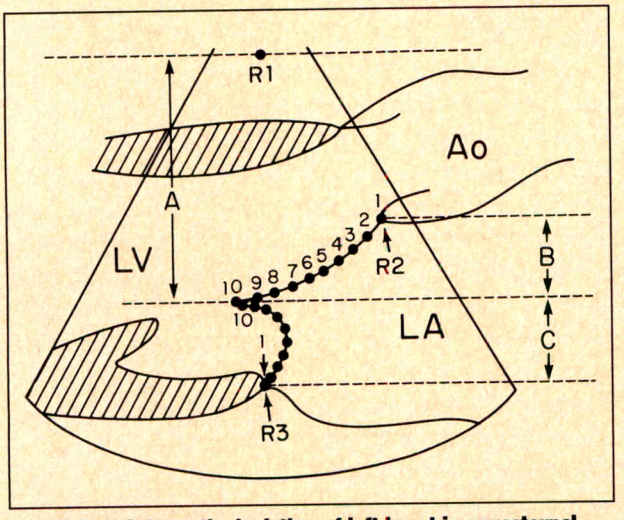


FIGURE 1. Schematic depiction of left heart in parasternal long-axis 2-dimensional echocardiographic view showing placement of 10 equally spaced points along mitral leaflets from their hinging points to tips (numbers 1 to 10, respectively). Using a computerized system, the position of each point was identified on sequential echocardiographic frames, and their motion in the y-axis was assessed compared with reference points at the transducer chest wall interface (R1), and anterior (R2) and posterior (R3) mitral leaflet hinging points. A = distance of anterior mitral leaflet tip from transducer-chest wall; B = anterior mitral leaflet hinging point; C = posterior mitral leaflet hinging point; Ao = aorta; LA = left atrium; LV = left ventricle.

Diagnosis of mitral valve prolapse: All diagnostic and quantitative evaluations of the mitral valve were performed blindly, with no knowledge of either clinical findings or results of the alternate 2-dimensional or M-mode echocardiographic technique. Standard criteria for M-mode echocardiographic diagnosis of MVP were used,[4,12,13] with 2-dimensional echocardiographic verification of correct beam angulation. As previously described,[4] diagnosis of MVP is made only when continuous mitral leaflet interfaces: (1) move ≥2 mm behind the C-D line for late systolic prolapse or ≥3 mm behind the C-D line for holosystolic prolapse, and (2) exhibit "turning around" with actual posterior motion away from the transducer.

For the time-motion reconstruction a criterion of posterior late systolic buckling or holosystolic hammocking ≥2 mm behind the line joining the vertical axis location of mitral leaflet closure and opening (similar to the C-D line of M-mode echocardiography) was used to diagnose MVP. The cardiac cycle digitized for

the display of 2-dimensional motion pattern was used for the reconstruction.

Diagnosis of mitral leaflet billowing: This diagnosis was made by 2-dimensional echocardiography when 1 or both mitral leaflets protruded across the plane of the mitral anulus into the left atrium in systole, as recommended by previous investigators[14,15] (Figure 2). As suggested by Levine et al,[11,16] only the parasternal long-axis view was examined for the diagnosis of MVP because the nonplanar shape of the mitral anulus can produce the appearance of MVP in the apical 4-chamber view in normal subjects.

Statistical analysis: Differences between 2 frequencies were evaluated by the chi-square test with Yate's continuity correction or the Fisher exact test. Comparison of continuous variables among groups was performed using analysis of variance with Scheffe post-hoc test, as was comparison of the degree of posterior mitral leaflet displacement compared to alternative reference points (chest wall, anterior and posterior end of mitral anulus) within groups of subjects. A p value <0.05 was considered statistically significant.

RESULTS

Real-time echocardiograms: As previously described,[7] digital analysis of 2-dimensional parasternal long-axis views demonstrated mitral leaflet billowing into the left atrium during systole in 24 of the 48 subjects with mitral prolapse (50% sensitivity) and in 0 of the 35 control subjects (100% specificity). M-mode criteria for MVP were met in all cardiac cycles and views visualizing the mitral valve in 20 of the 24 subjects with, but in only 4 of the 24 subjects without, leaflet billowing (chi-square = 18.75, $p<0.00002$).

Computer-reconstructed time-motion displays: Posterior systolic displacement (with respect to the chest wall) of the posterior mitral leaflet in reconstructed tracings met our criteria for the diagnosis of MVP in 4 of the 35 normal subjects (11%); in all these subjects the reconstructions were normal when the posterior leaflet hinging point was used as the reference point for measurement of anteroposterior displacement of the mitral leaflets. Moreover, in all these subjects, the reconstructed tracings exhibited the same posterior displacement for all 10 equidistant points along the posterior leaflet, supporting the inference that the MVP appearance was due to posterior displacement of the posterior end of the mitral anulus. The time-motion reconstruction tracings were diagnostic for MVP in all 24 patients (100%) with mitral leaflet billowing (Figure 3) and in 20 of 24 subjects (83%) without leaflet billowing (Figure 4) (both $p<0.0000002$ vs controls). When the systolic mitral leaflet movements were reconstructed using the posterior leaflet's hinging point as the reference point, 20 of the 24 patients (83%) with billowing continued to exhibit MVP ($p<0.0000001$ vs controls), whereas 14 of the 24 patients (58%) without billowing had MVP by time-motion reconstruction ($p<0.002$ vs controls; p =not significant between the 2 groups with MVP). When the hinging point of the anterior leaflet was used as the reference point, 22 of the 24 patients (92%) with billowing ($p<0.00001$ vs controls) continued to exhibit MVP, as did 19 of the 24 patients (79%) without billowing ($p<0.0005$ vs controls).

The maximal degree of systolic posterior displacement of the anterior and posterior mitral leaflet was also considered as a continuous variable (Table I). With the chest wall location of the echocardiographic

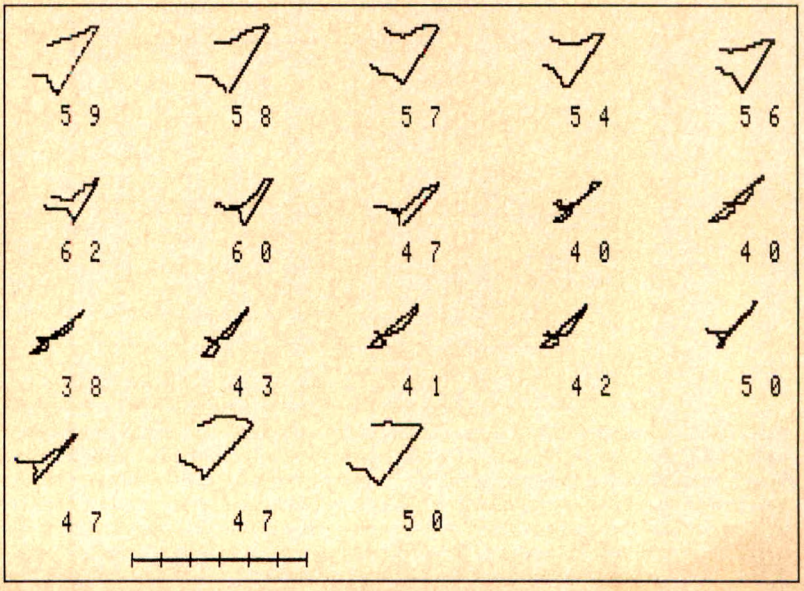


FIGURE 2. Computer printout of frame-by-frame contours of mitral leaflets and anulus in patient with mitral prolapse and leaflet billowing. Frames are displayed in their original orientation; both anterior and posterior mitral leaflets can be seen to protrude across the plane of the mitral anulus in systole. The calibration in centimeters is displayed at the bottom; the inclination of the mitral anulus in degrees from the horizontal is indicated below each frame.

transducer as the reference point, MVP patients both with and without leaflet billowing had substantially greater posterior displacement of mitral leaflets in time-motion reconstruction tracings than normal subjects; similar results were obtained when the anterior end of the mitral anulus was selected as the reference point. When the posterior end of the mitral anulus was used as the reference point, the MVP patients with billowing had the same degree of systolic displacement of the posterior leaflet as with the chest wall as reference point, whereas the MVP patients without billowing had a significant ($p < 0.02$) reduction of posterior displacement of the posterior leaflet. In both subgroups of patients with MVP, the time-motion reconstruction tracing, independent of the reference point selected for the computer reconstruction, exhibited the greatest posterior displacement in the midportion of the mitral leaflets.

DISCUSSION

The present study demonstrates that the M-mode echocardiographic appearance of MVP can be due either to mitral leaflet billowing into the left atrium (a predominately superior motion) or to posterior displacement of the leaflets due to expansion of the mitral anulus during systole. In fact, computer reconstruction of time-motion tracings from a single cardiac cycle met standard M-mode criteria for MVP in all 24 of our patients with 2-dimensional mitral leaflet billowing (100%) and in 20 of the 24 patients (83%) without leaflet billowing but with exaggerated expansion of the mitral anulus during systole. These results were confirmed when the hinging point of the anterior mitral leaflet was used as a reference point for assessment of anteroposterior motion of the leaflets, thus excluding a significant impact of overall heart motion on our findings.

When the posterior end of the mitral anulus was used as an intracardiac reference point, 20 of 24 patients with billowing continued to exhibit an abnormal time-motion reconstructed tracing, indicating that M-mode evidence of MVP is independent of mitral anular dynamics in patients with the leaflet billowing form of MVP. Conversely, 10 of the 24 patients with nonbillowing MVP (42%) had normal reconstructed tracings when the posterior end of the mitral anulus was used as the reference point, supporting our previous interpretation[7] that the M-mode echocardiographic appearance of MVP in patients without systolic protrusion of the mitral leaflets into the left atrium was related to exaggerated systolic expansion of the mitral anulus with posterior displacement of the entire mitral valve apparatus. Of note, mitral leaflet displacement in recon-

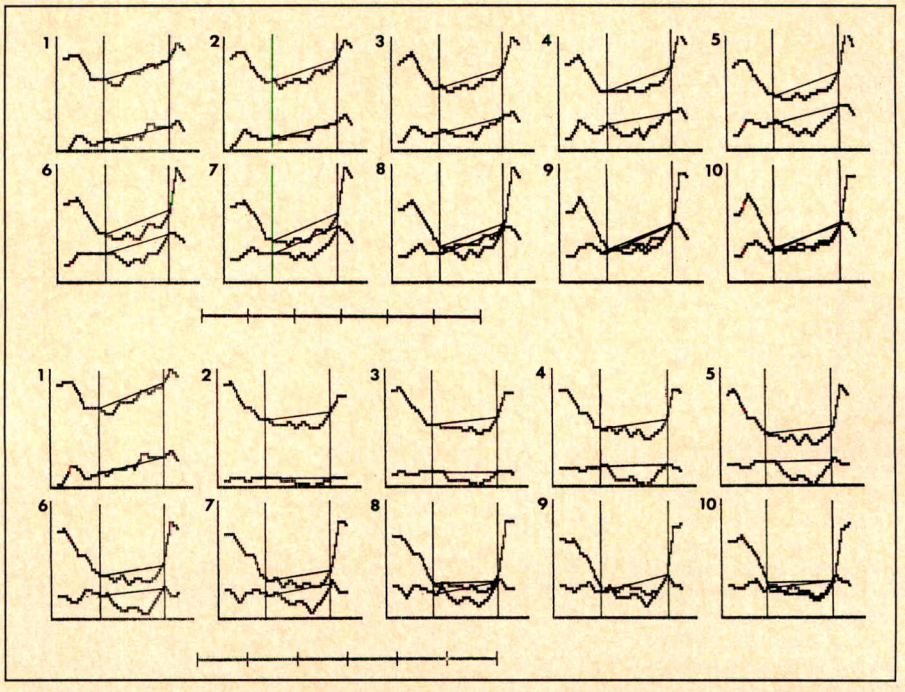


FIGURE 3. Computer time-motion reconstruction derived from the 2-dimensional echocardiographic images displayed schematically in Figure 2. In each panel, 10 plots represent vertical distance from transducer in systole of 10 points equally spaced along length of each leaflet (from base to tip). *Top,* with transducer as reference point, posterior displacement of both leaflets by >2 mm in late systole is clearly shown in plots 2 to 10. In each plot, *vertical lines* indicate times of mitral leaflet closure and opening; *horizontal lines* connecting closure and opening points are similar to C-D line of M-mode echocardiography. *Bottom,* with posterior end of mitral anulus as reference point, posterior displacement of both leaflets by >2 mm in late systole shown in plots 2 to 8. Calibration in centimeters is displayed at bottom.

TABLE I Posterior-Directed Mitral Leaflet Displacement Measured by Time-Motion Reconstructed Echocardiography

		Patients with Mitral Valve Prolapse				
	Normal Subjects (n = 35) (a)	a vs b p<	With Leaflet Billowing (n = 24) (b)	b vs c p<	Without Leaflet Billowing (n = 24) (c)	a vs c p<
Anterior mitral leaflet						
Versus chest wall (mm)	0.61 ± 0.82	0.0005	3.48 ± 2.57	NS	2.87 ± 2.20	0.0005
Versus anterior end of mitral anulus (mm)	0.91 ± 1.09	0.0005	3.10 ± 2.60	NS	2.33 ± 1.86	0.025
Versus posterior end of mitral anulus (mm)	0.77 ± 0.91	0.0005	3.32 ± 2.74	NS	2.23 ± 2.39	0.025
Posterior mitral leaflet						
Versus chest wall (mm)	0.98 ± 1.31	0.0005	3.94 ± 1.84	0.05	2.70 ± 1.64	0.005
Versus anterior end of mitral anulus (mm)	1.44 ± 1.35	0.0005	3.89 ± 2.66	0.05	2.55 ± 1.83	0.05
Versus posterior end of mitral anulus (mm)	0.38 ± 0.78*	0.0005	3.58 ± 1.80	0.0025	1.55 ± 1.48†	0.05

Statistical significance of posterior mitral leaflet displacement: *p <0.05 compared with motion versus chest wall, p <0.0002 compared with motion versus anterior end of mitral anulus; †p <0.02 compared with motion versus chest wall, p <0.05 compared with motion versus anterior end of mitral anulus.
NS = not significant.

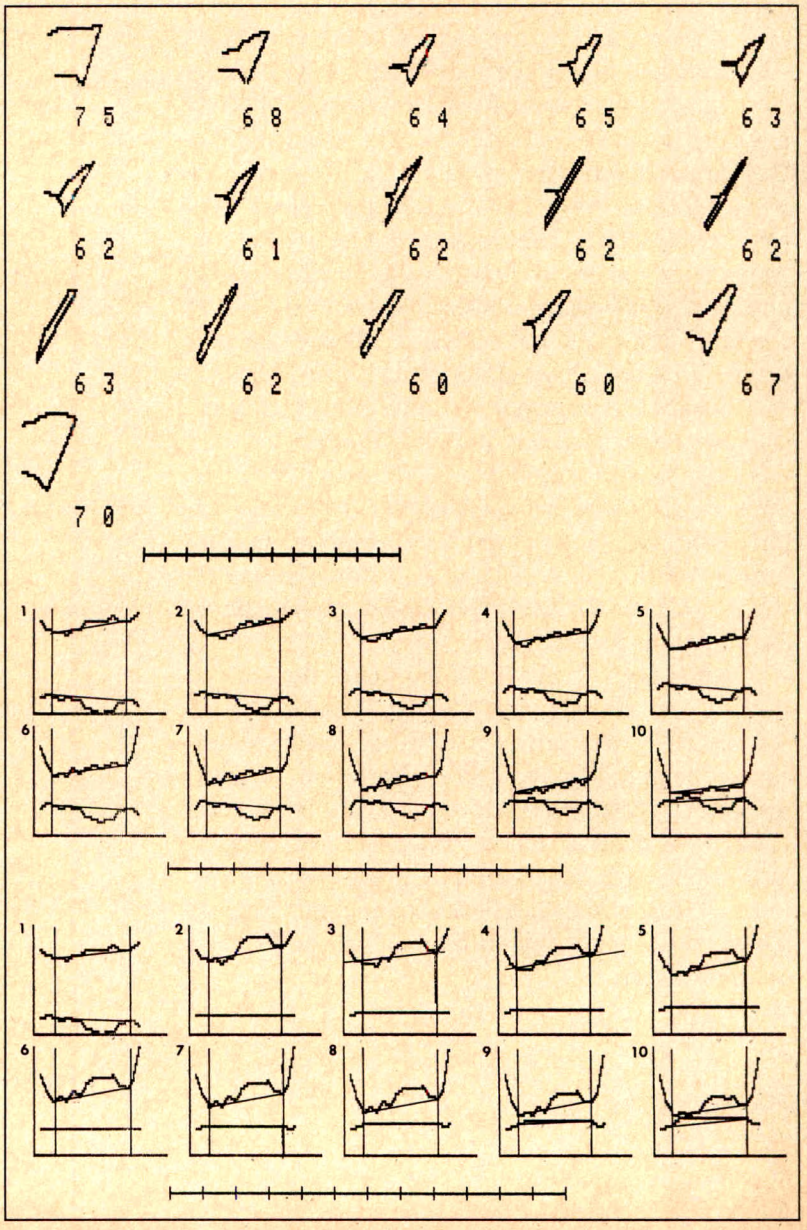


FIGURE 4. Computerized representation of 2-dimensional echocardiographic images and time-motion reconstruction of anterior and posterior mitral leaflet motion from patient with M-mode mitral valve prolapse without leaflet billowing. *Top,* mitral leaflets do not cross plane of mitral anulus in any frame during systole. *Middle,* with transducer as reference point, posterior systolic displacement of both mitral leaflets exceeds 2 mm. *Bottom,* with posterior end of mitral anulus as reference point, there is no significant posterior displacement of either mitral leaflet.

structed tracings tended to be of greater magnitude in patients with MVP who exhibited leaflet billowing, in parallel with evidence that most patients with clinically severe MVP have this pattern of abnormal mitral leaflet motion.[17] The observation that 20 of the 24 subjects with leaflet billowing met the M-mode criteria for MVP in each cardiac cycle in all views, whereas 20 of the 24 subjects without billowing had MVP in some cycles but not others ($p < 0.001$) is compatible with a dynamic mechanism of MVP in the latter group and to a fixed anatomic abnormality in the former one.

Discordance among echocardiographic methods: The absence of MVP in the time-motion reconstruction of a small group (4 of 24 or 17%) of patients without leaflet billowing may reflect methodologic differences between real-time M-mode echocardiograms and computer-reconstructed time-motion tracings: Each reconstruction was derived from a single 2-dimensional cardiac cycle, and review of the extensive M-mode mitral valve recordings in these 4 patients revealed MVP on some but not other cardiac cycles. The selection of the 2-dimensional echocardiographic cycle for computerized analysis was based exclusively on the superior technical quality of the 2-dimensional images without any requirement concerning motion of the mitral leaflets or anulus; this methodology allowed blind interpretation of the echocardiograms but may have allowed use of a cardiac cycle or imaging of the mitral leaflets in a plane that would have generated a normal M-mode tracing. The use of simultaneously recorded M-mode and 2-dimensional images would allow the selection of a cardiac cycle with M-mode findings diagnostic of MVP to permit verification of this hypothesis. However, this approach would prevent blinding of the time-motion reconstruction and 2-dimensional interpretation to the results of M-mode recordings.

Conclusions: Computer-reconstructed time-motion displays demonstrated that (1) the M-mode appearance of MVP may be related either to systolic protrusion of the mitral leaflets into the left atrium or to exaggerated systolic expansion of the mitral anulus, and (2) in MVP patients without leaflet billowing, exaggerated anular expansion contributes to posterior displacement of the mitral valve with consequent posterior movement of the leaflets as recorded on the M-mode echocardiogram.

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Radiation Exposure of Pediatric Patients and Physicians During Cardiac Catheterization and Balloon Pulmonary Valvuloplasty

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Thermoluminescent dosimeters were applied to various areas of 61 pediatric patients and physicians to measure radiation doses during routine cardiac catheterization and during 4 cases of balloon pulmonary valvuloplasty. Radiation doses were measured during chest roentgenography, fluoroscopy and cineangiography. Average skin dose to the chest was 121 μGy during chest x-ray, 5,182 μGy during catheterization and 641 mGy during valvuloplasty. For the eyes, thyroid and gonads of the patients, the exposure during routine catheterization was equal to 0.4, 6 and 0.2 chest x-rays, respectively. Radiation dose of the operator was 3 μGy for the eyes and 6 μGy in the thyroid. About 56% of the operator's dose could be reduced by thyroid shields, and 80% by lead aprons. The assistant received only 1 μGy outside the thyroid shield. Therefore, we have concluded that the patients' dose during routine catheterization is largely based on our experimental results, but the dose is acceptable based on the risk factor analysis. The skin dose to the right lateral chest of the patient during valvuloplasty is extremely high, perhaps as high as the equivalent of 1,000 chest x-rays. Besides the clinical benefits of valvuloplasty, the long-term radiation-related hazards to the patient should be carefully monitored.

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Several investigations have examined the radiation dosage received by patients and physicians during cardiac catheterization.[1–9] Recently, interventional cardiac catheterization has developed rapidly, and has been applied worldwide in the treatment of moderately severe valvular pulmonary stenosis and a variety of congenital heart diseases.[10,11] Although many studies have been published on its clinical applications and complications, the problems regarding radiation hazards have never been addressed.[12] In this study, we measured various radiation doses to pediatric patients and the physicians performing cardiac catheterization, and evaluated the risks to radiosensitive organs. Preliminary results of radiation dose during balloon pulmonary valvuloplasty are also presented.

METHODS

Between January 1989 and June 1990, 61 infants and children chosen at random were evaluated during clinically indicated cardiac catheterization studies. Their ages ranged from 28 days to 15 years (mean 4.7 years). Thirty-six had left to right shunts, 9 had cyanotic congenital heart disease, 10 had obstructive heart disease and 6 had Kawasaki disease. All underwent complete 2-dimensional echocardiographic study before catheterization; all patients had right- and left-sided cardiac catheterizations, which were performed percutaneously from the right groin area. Cardiac catheterization was performed in the standard fashion.[1] A single-plane U-arm televised fluorocinescopy (Toshiba KX-1250) was used. It consisted of an undercouch tube and an overcouch dual-mode image intensifier. There was no protective ceiling shield between the table and the operator. The distance from focus to table top was 75 ± 4 cm, and the total filtration in the beam was 1.1 mm aluminum. The fluoroscopic field size ranged from 132 to 256 cm^2. During fluoroscopy the nominal voltage was in the range of 60 to 89 kV, with a tube current from 0.4 to 1.0 mA. During cineangiography, the corresponding values were 60 to 66 kV, and 250 to 400 mA, respectively. Cineangiograms at a filming speed of 60 frames/s were performed as clinically indicated. To reduce exposure to scattered radiation, during cineangi-

TABLE I Entrance Skin Dose Over the Organs of the Pediatric Patients During Each Cardiac Catheterization and Cineangiography (μGy for examination)

Age (yr)	No. of Pts.	Time: Fluoro +Cine (min)	Time: Cine (sec)	Eye	Thyroid	Midsternum: Fluoro +Cine	Midsternum: Cine	Right Lateral Chest: Fluoro +Cine	Right Lateral Chest: Cine	Umbilicus	Gonad
<2	23	6 ± 4	6 ± 5	63 ± 47	877 ± 694	5,517 ± 3,183	3,107 ± 1,676	11,864 ± 5,402	7,637 ± 4,326	144 ± 62	31 ± 24
2–6	21	5 ± 2	11 ± 4	57 ± 52	586 ± 458	6,569 ± 4,762	3,337 ± 2,559	11,338 ± 6,489	7,710 ± 4,828	113 ± 62	17 ± 16
>6	17	6 ± 4	10 ± 4	35 ± 40	472 ± 318	3,014 ± 1,810	1,821 ± 1,128	6,984 ± 4,912	4,453 ± 3,759	105 ± 60	12 ± 7
Total	61	6 ± 5	11 ± 5	51 ± 46	764 ± 558	5,182 ± 3,815	2,828 ± 2,017	10,098 ± 6,048	6,448 ± 4,019	123 ± 64	24 ± 20

The radiation dose ratio during cineangiography compared with that during fluoroscopy and cineangiography is 61% at sternum and 70% at right lateral chest.
Cine = cineangiography; Fluoro = fluoroscopy.

ography all personnel stood ≥2 meters away from the table.

Thermoluminescent dosimeters were applied to the body to measure radiation exposure during cardiac catheterization. Each dosimeter contained 80 mg of dehydrated powder of highly sensitive dysprosium-activated calcium sulfate that was sealed in a 0.3 × 0.1 × 2.0 cm black polyethylene cylindrical tube.[13] Precatheterization chest roentgenography was performed in all children, and dosimetry was measured in 22. During hemodynamic assessment, the dosimeters were located on the skin over the glabella, thyroid, midsternum, right lateral chest, umbilicus and pubic area of the patient. During cineangiography, unexposed dosimeters were added to midsternum and the right lateral chest. For the operator, the dosimeters were put on the glabella, left third finger, left knee area outside the apron, the thyroid area inside and outside the shield, the umbilical area inside and outside a full wraparound apron of 0.5-mm thickness. For the assistant, standing to the right of the operator, the dosimeter was located outside the thyroid shield. The dosimeters were prepared, processed and read as previously reported.[14] Using the peak of the glow curve, they were read out on a Harshaw 2000 B & C Reader. The reader stability was ± 0.8%. The total error of the reader system in μGy was ±3.0%.

Another 4 children with pulmonary stenosis, whose mean pressure gradient was 67 mm Hg, were also enrolled in this study to measure the radiation exposure of the sternum and right lateral chest during routine catheterization, angiography and balloon pulmonary valvuloplasty. After a lateral projection of right ventriculography, valvuloplasty was then performed 2 to 3 times using the technique described by Lababidi and Wu.[11] After dilation, the balloon catheter was removed and pressure measurements were repeated. Finally, a post-dilation right ventricular angiography was performed again.

RESULTS

The mean fluoroscopic time was 6 ± 5 minutes. The number of cineangiograms performed varied with the complexity of the lesion. Most children had 2 single-plane cineangiograms. The mean cineangiographic time was 11 ± 5 seconds. Average skin dose over the organs of the patients during the complete catheterization study (fluoroscopy plus cineangiography) are listed in Table I. In the midsternum and right lateral chest area, cineangiography contributed 61 and 70% of total radiation dose during complete catheterization, respectively.

The correlation analysis of radiation dose at midsternum area was calculated by the Pearson correlation method. Figure 1 implies a weak negative linear relation ($r = -0.39$, $p < 0.01$) between fluorocineangiographic radiation dose and patient age. However, radiation dose has no significant relation to cinefluorographic time ($r = 0.14$, $p > 0.05$) (Figure 2). In Figure 3, the radiation dose shows a clear correlation with cine time ($r = 0.64$, $p < 0.01$).

Precatheterization chest roentgenography was performed in all children; dosimetry was measured in 22 children. Average skin dose to the chest was 121 ± 27 μGy. As a means of comparison, the radiation dose on the skin over the organs was expressed as chest x-ray equivalents, defined as the ratio of the skin dose over the organ of interest to that over the chest. When so expressed (Table II), the fluoroscopic phase of the chest area was equal to an average of 43 chest x-rays, whereas cineangiography was equivalent to an average of 23 chest x-rays. In cases of complete cardiac catheterization, the average thyroid dose was equivalent to 6 chest x-rays. That value of the right lateral chest, umbilicus and gonads was equivalent to 83, 1.2 and 0.2 chest x-rays, respectively.

The doses of the operator and the assistant are given in Table III. The left knee of the physician received highest exposure during catheterization. The doses on

different sites of the operator's body and that of the assistant were relatively small in terms of chest x-ray equivalents. The radiation exposure outside/inside of the thyroid shield was 6/3 μGy. In other words, about 56% of the radiation exposure could be reduced by the thyroid shield. The value outside/inside of the lead apron in the umbilical area was 7/2 μGy. For the body, about 80% of the exposure could be reduced by using wraparound aprons.

In valvuloplasty, the mean time of fluoroscopy was 28 minutes and the mean time of cineangiography was 63 seconds. The radiation dose to the sternum and right

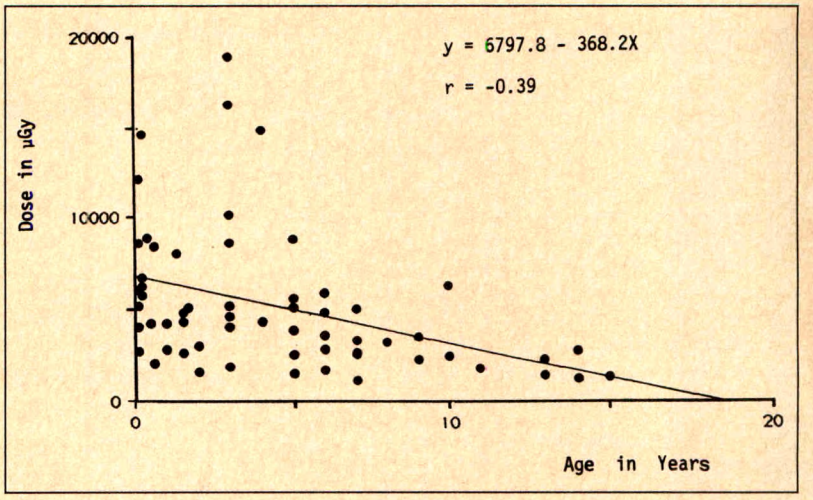


FIGURE 1. Relation between patient's age and fluorocineangiographic radiation dose at midsternum.

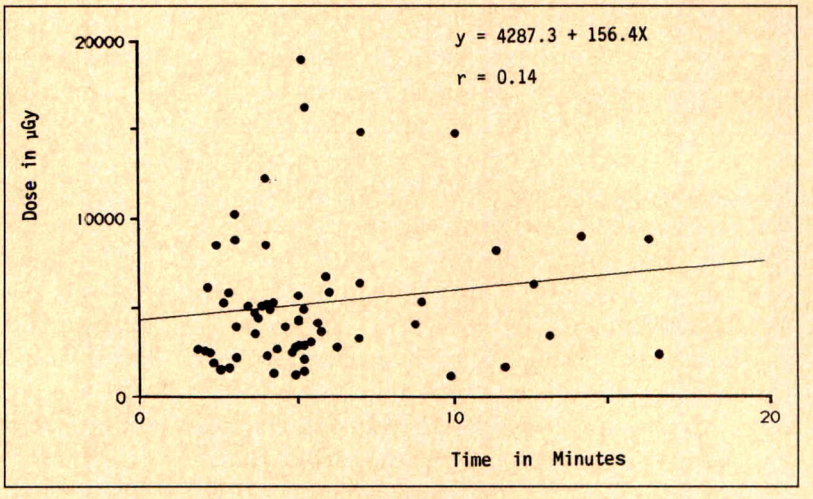


FIGURE 2. Fluorocineangiographic time versus dose at midsternum.

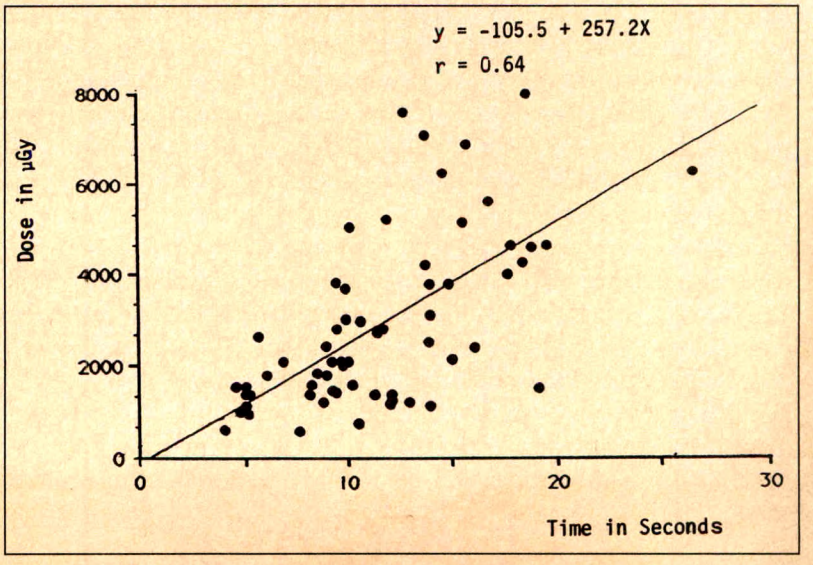


FIGURE 3. Cineangiographic time versus dose at midsternum.

TABLE II Chest X-Ray Equivalents of the Skin Dose Over the Organs of Patients During Cardiac Catheterization and Balloon Pulmonary Valvuloplasty

Radiation Profiles	Average Dose (μGy)	Equivalent No. of Chest X-Rays
Skin dose of the chest during		
Chest x-ray	121	1
Complete catheterization	5,182	43
Cineangiography	2,828	23
Dose during complete catheterization		
Eyes	51	0.4
Thyroid	764	6
Right lateral chest	10,098	83
Umbilicus	123	1
Gonads	24	0.2
Dose during BPV		
Sternum	64,120	530
Right lateral chest	125,460	1,037

BPV = balloon pulmonary valvuloplasty.

TABLE III Measured Radiation Exposure of the Physicians During Each Cardiac Catheterization (μGy per examination)

		Thyroid		Umbilicus			
Personnel	Eyes	Outside Shield	Inside Shield	Outside Apron	Inside Apron	Left Third Finger	Left Knee
Operator	2 ± 3	6 ± 3	3 ± 2	7 ± 3	2 ± 2	8 ± 4	34 ± 19
Assistant	—	1 ± 2	—	—	—	—	—

Radiation exposure is reduced 56% by the thyroid shield, and radiation to the umbilical area is reduced 80% by using lead apron.

lateral chest was 641 and 1,254 mGy, respectively. The dosage, changed to chest x-ray equivalents, is shown in the lower rows of Table II.

DISCUSSION

The purpose of cardiac catheterization is to examine the heart, but the resultant x-ray dose to the chest is large. Malsky et al[15] suggest that dosimetry information should be obtained during an actual catheterization rather than in a phantom procedure. Our reports (Table I) indicate a wide range of variation in patients' doses. This may be due to variation in fluoroscopy and cine exposure time owing to the variable complexity of congenital heart disease, the wide range of patients' ages and body sizes, and the variable positioning of the dosimeter. The smaller the patient, the more radiation dose he receives (Figure 1). The radiation dose is proportional to cineangiographic time (Figure 3), but is not well correlated with fluorocinescopic time (Figure 2). The fact that right lateral chest area received the largest dose in this study might be due to the undercouch x-ray tube, and because the angulations used in cineangiography were mostly left lateral or 4-chamber projections. During these views, the x-ray tube was located close to the right lateral area of the patients' chests.

TABLE IV Estimated Risk Factor of Patient Mortality* from Radiation Exposure During Cardiac Catheterization

Organ	Paragraph in ICRP #26	Radiation Risk per Sievert	Absorbed Dose of Pt. (μGy)	Mortality per 10^6
Hereditary effect (gonads)	60	4×10^{-3}	24	0.01
Red bone marrow (leukemia)	44	2.0×10^{-3}	5,182	10
Thyroid (carcinoma)	56	0.5×10^{-3}	764	0.4

*Calculated for specific organ from data in No. 26 of the International Commission on Radiological Protection (ICRP).[18]

These experimental results show that the doses we obtained were of a low level compared with those of other investigators.[6–8,16] This might be due to several factors: We used different radiographic equipment; each of our cases had a complete echocardiographic study before catheterization; the catheterization was performed by an experienced doctor; the heart diseases studied were relatively less complex; and the fluoroscopic field size was properly coned. These minimized the fluoroscopic time and the need for cineangiography.

The dose equivalent is defined as[17] $H = D \times Q \times N$ where H is the dose equivalent, D the absorbed dose, Q the numerical quality factor (=1), and N the product of the other modifying factors (=1). From No. 26 report of the International Commission on Radiological Protection,[18] the risk factor for thyroid is 0.5×10^{-3} per sievert (Sv), so that the risk of death from thyroid cancer (Table IV) is $H = 745 \times 10^{-6}$ Sv $\times 0.5 \times 10^{-3}$ $Sv^{-1} \times 1 \times 1 = 0.4$/million. The risk of mortality from leukemia is estimated to be 10/million. The hereditary effect is negligible at 0.01/million.

The operator performing cardiac catheterization receives a relatively significant dosage of radiation.[2,4,5] Exposure of the legs to scattered radiation received the highest radiation doses as reported by others[19] and by us (Table III). However, this is not so critical owing to their decreased radiation sensitivities.[20] Exposure of the trunk is also not so critical, because the universal use of adequate lead aprons reduces the exposure to radiation by 60 to 90%.[2,5] The radiation dose to the trunk measured inside the apron was very small, being 4 μGy/exam without shield between the table and the doctor, but <1 μGy/exam with the shield.[5] Our data (Table III) also demonstrate a low dose, 7 μGy/exam outside the apron. However, it was 2 μGy/exam inside the lead apron, a reduction of 80% in dose. In approximately one-third of the doctors examined in our study, the dose of the trunk inside the apron was <0.1 μGy/exam.

When considering limiting the occupational exposure of physicians to radiation, one must be concerned about the exposure of the lens of the eye, and the possi-

bility of radiation-induced cataracts. The radiation to the operators' eyes range from 1 to 180 μGy/exam.[3–5,19] Balter et al[5] suggested that radiation-induced cataracts were not very likely if a doctor's accumulative exposure is at a rate of 0.15 Gy/year for an entire 40-year work life. Radiation-induced neoplasia of the thyroid gland of personnel is another area that should be considered.[20] The exposure of the thyroid during catheterization by a doctor ranged from 35 to 300 μGy/exam in other studies[3–5,21] and 6 μGy/exam in ours. The maximal permissible dose was 3 mSv/week[21]; thus, the risks of radiation-induced thyroid neoplasia appear to be negligible in our studies.

For years, balloon pulmonary valvuloplasty has been accepted as an effective means of reducing pulmonary outflow gradients in pediatric patients with valvular pulmonary stenosis.[10–12] The procedure has been proven safe, with a lower mortality than surgery and probably an overall lower morbidity as well.[22] Nevertheless, it is sometimes very difficult to manipulate the guidewire and the big balloon across the stenotic pulmonary valve. This means that more time is needed in fluoroscopy for this procedure than in routine catheterization. Our survey discloses a relatively large dose of radiation (Table II). The skin dose of the chest might be as much as 10 times higher than that during routine catheterization, or the equivalent of 1,000 chest posteroanterior roentgenograms. The value is tremendously higher for growing children. However, during the follow-up period, the 4 patients had normal leukocyte counts and external appearances, and their chromosome studies 3 to 6 months after valvuloplasty revealed no aberrations.

The procedure can be successfully performed in cases of critical neonatal pulmonary stenosis with good short-term results.[23] This report indicates that it lasted 2 to 4 hours with a total fluoroscopy time of 30 to 68 minutes. In this preliminary study, the number of cases studied may be too small to form a conclusion about the radiation hazards of valvuloplasty. However, based on our results of 60 to 70% of radiation dose during catheterization arising from cineangiography, we would suggest minimizing the number of cineangiographic films or reducing the filming rate whenever possible. Before more information is obtained, one should pay greater attention to the probable effects of radiation-related complications of balloon-directed valvuloplasty in pediatric patients.

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Role of Angioscopy in the Treatment of Peripheral Vascular Disease with Percutaneous Atherectomy

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The role of adjunctive video angioscopy was evaluated in 43 patients with symptomatic peripheral vascular disease undergoing percutaneous atherectomy with the Simpson atherocath. There were 57 target lesions (superficial femoral, n = 46; popliteal, n = 11) of which 33 were stenotic (86 ± 11%) and 24 were total occlusions of 0.5 to 10.6 cm in length, determined by angiography. Intraluminal inspection, with angioscopes of 0.85 to 1.5 mm in outer diameter housed within a guide catheter, could be performed in 55 of 57 lesions (96%) before atherectomy and in 39 of these 55 (71%) after atherectomy. Failure to obtain an adequate image was usually due to insufficient irrigation, especially in recanalized vessels. In 13 of 23 successfully recanalized arteries (54%) the occlusion could be crossed by the angioscope itself, whereas in 10 cases (42%) a guidewire or a sheath introducer was necessary. Angioscopic passage revealed that often long total occlusions, determined by angiography, consisted of ≥1 discrete occlusion with interposed patent thrombus-free vascular segments. After atherectomy, in 15 instances with an acceptable angiographic result, angioscopy was helpful in identifying residual plaques and flaps which then selectively underwent atherectomy. In conclusion, angioscopy proved to be a useful adjunct to angiography in optimizing vascular recanalization with percutaneous atherectomy.

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With the advent of new therapeutic interventional techniques, which may be specific for the treatment of spontaneous or iatrogenically induced vascular lesions, the need for improved diagnostic techniques has emerged. Several reports emphasize the value of direct intraoperative visualization of the vessel interior in guiding surgical endarterectomy, laser angioplasty, balloon angioplasty and to assess the anastomotic sites during vascular bypass surgery.[1–8] This report evaluates the potential advantage of direct percutaneous angioscopy to angiography in guiding therapy with the Simpson atherocath.

METHODS

Patients: Angioscopy was performed in 43 patients (aged 38 to 89 years) who had been accepted for percutaneous atherectomy (Peripheral Simpson Atherocath, 7Fr and 9Fr; DVI Inc., Redwood City, California) as treatment of symptomatic peripheral vascular disease. Thirty-nine patients (90%) presented with moderate to severe claudication, 2 (5%) had pain at rest and 2 (5%) had gangrene. Mean standardized walking distance before intervention was 79 ± 60 m. The distribution of vascular lesions by angiography included 33 stenoses (86 ± 11%) and 24 total occlusions (Table I). The indications for the procedure included symptoms of Fontaine class II or greater and vessel narrowing of ≥70% (coexisting narrowings >60% were treated along with the target lesion). The length of the total occlusions were defined angiographically as the distance between the proximal cutoff and the distal point of reemergence of the vascular continuation, and ranged from 0.5 to 10.6 cm (mean 3.7 ± 2.8 cm). This study was approved for human investigation by the ethics committee of the Department of Medicine, University of Munich. Informed consent was obtained from each of the 43 patients on the day before the intervention.

Description of procedure: All patients were treated with 0.5 g of aspirin daily beginning 1 day before and continuing for 6 months after atherectomy. All patients were brought to the catheterization laboratory after an overnight fast. The appropriate femoral artery was cannulated in an anterograde fashion and a 9Fr sheath was placed. Then 10,000 IU of heparin was given intrave-

nously. After routine angiography, the angioscope was advanced through the sheath until the vascular obstruction was visualized. Qualitative evaluation of the vascular lumen including stenosis morphology was then performed. In cases of total occlusion, the scope was advanced cautiously in an effort to cross the lesion. If the lesion could not be crossed, the angioscope was removed and a guidewire or sheath introducer was used to traverse the occlusion. After recanalization, atherectomy as previously described was performed.[9,10] The angioscope was then reinserted and the treated intraluminal sites were inspected. If the angioscopic view found the remodeled lumen obstructed by residual plaque material or by large intimal flaps, these sites underwent repeat atherectomy.

Angioscopic equipment: Flexible fiberoptic endoscopes (Miniflex angioscopes, Baxter Inc.) of 0.85, 1.0 and 1.5 mm of outer diameter were used. The 0.85- and 1.0-mm angioscopes were coaxially guided by a cut x-ray dense Cournand catheter or a special guide catheter with an inflatable balloon at its distal tip (Baxter Inc.). In a small number of patients the balloon was inflated in an attempt to limit blood flow and improve intraluminal visualization. However, this was not found to be beneficial. To ensure a sufficient field of view, constant irrigation was achieved through the guide catheter. The flow of the pressurized saline perfusion system was regulated as needed. In the last 26 patients (34 lesions) the 1.5 mm angioscope was used exclusively and normal saline was intermittently delivered through the integrated irrigation channel by way of a roller pump (Ureteromat, Storz Inc., Federal Republic of Germany). The rate of saline delivery was based on the angioscopic view and did not exceed a total volume of 600 ml per patient. Manual compression of the ipsilateral femoral artery, by decreasing blood flow, helped to reduce the volume of irrigant fluid needed.

Intravascular illumination was provided by a 250-W cold light (Baxter Inc.). The lens system at the proximal end of the endoscope was coupled to a miniature video camera (Endovision 533, Storz Inc.) and images obtained were then relayed to a high-resolution color video monitor. Continuous recordings of the entire angioscopic procedure were made using a video cassette recorder (U-matic VO-5800 PS, Sony Inc.).

RESULTS

In 43 patients with a total of 57 symptomatic lesions of the superficial femoral and popliteal arteries (Table I), percutaneous angioscopy was performed before and after percutaneous atherectomy as an adjunct to routine angiography. Time required for endoscopic examination did not exceed 10 minutes before or after atherectomy. Complications such as distal embolization, arterial perforation or volume overload of the patient were not observed. Good quality angioscopic images were obtained in 55 of 57 target lesions (96%) before and in 39 of these 55 lesions (71%) after atherectomy. Unsuccessful attempts before atherectomy were due, in 1 patient, to detachment of the proximal optical lens, probably caused by the high pressure used during sterilization, and in the other patient, to nonsterility of the angioscope during the procedure. After atherectomy, inspection of 4 sites could not be performed because of loss of equipment sterility. In 12 patients a blood-free visual field after atherectomy could not be obtained due to the improved arterial flow.

TABLE I Target Lesion Distribution (n = 57)

Characteristic	Superficial Femoral Artery	Popliteal Artery	Total
Stenoses (no.)	26	7	33/58%
% Stenosis (SD)	85 (11)	88 (12)	86 (11)
Occlusions (no.)	20	4	24/42%
Mean length (cm) (SD)	3.6 (2.9)	3.9 (2.0)	3.7 (2.8)
Range (cm)	0.5–10.6	1.8–6.5	0.5–10.6

SD = standard deviation.

In the non-target areas, preatherectomy, direct angioscopic inspection revealed diffuse vascular alterations ranging from low-profile atherosclerotic plaques to rough, partially ulcerated areas adjacent to normal segments with smooth intimal surfaces. Degree and distribution of these endoscopically detected luminal irregularities were not found by routine angiography.

On inspection of the target stenoses, the cross-sectional angioscopic view enabled us to characterize the local intraluminal pathology. Lesions were composed of smooth, white glistening atherosclerotic plaques and irregular stenosing tissue (Figure 1). In only 1 instance was a fresh red thrombus found obliterating the residu-

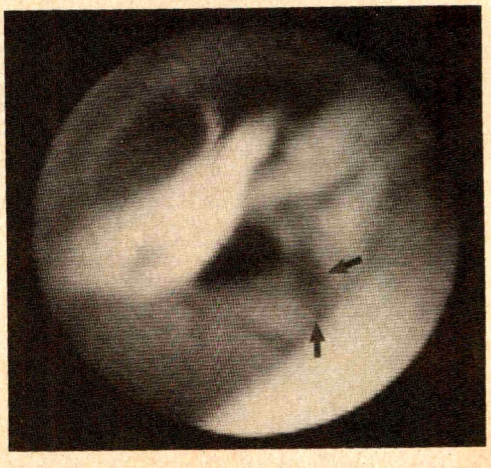


FIGURE 1. Photomicrograph of high-grade stenosis demonstrating irregular ulcerated plaque and small thrombus *(arrow).*

TABLE II Recanalization of Total Occlusions (n = 24)			
Outcome	Mode	No.	%
Success		23	96
	Guide catheter + angioscope	13	54
	Guidewire/sheath introducer	10	42
Failure		1	4

al lumen of a subtotaled femoral artery; organized thrombus could not be identified. In addition, we could not reliably detect calcifications in the obstructing tissue or differentiate between primary and restenotic lesions. Angioscopic evaluation of the stenotic diameter was not performed, because the device could not be reliably centered.

In totally occluded arteries, the cross-sectional endoscopic view revealed only glistening plaque totally obstructing the field of view. In one case the total occlusion was valve-like, and easily opened with a guidewire (Figure 2). Fresh red thrombus of sufficient size to be detected by the use of the angioscope was seen in only 1 case. In the 24 cases of total occlusion, advancement of the angioscope was attempted in an effort to apply gentle pressure to the obstructing plaque. With this technique, there were no cases of perforation or severe dissection leading to acute vessel closure. An all-white image obtained on the monitor signaled that the lens was in direct contact with the lesion. In 13 of 24 occlusions (54%), the angioscope was able to disrupt and push aside the obstructing plaque. Of the remaining 11 occlusions, 10 (42%) could be crossed by a guidewire or a sheath introducer. In 1 case (4%), only the initial portion of a total occlusion (5.2 cm in length) could be entered (Table II). As noted, when engaging obstructing plaque, the angioscope revealed an all-white image. Further advancement of the angioscope through these long occlusions revealed multiple segmental stenoses separated by nonpulsatile, relatively normal-appearing vascular wall. On traversing the most distal occlusion, blood flow and vascular pulsations were restored. With the return of blood flow, the intraluminal view immediately deteriorated. Without exception, the angioscopic

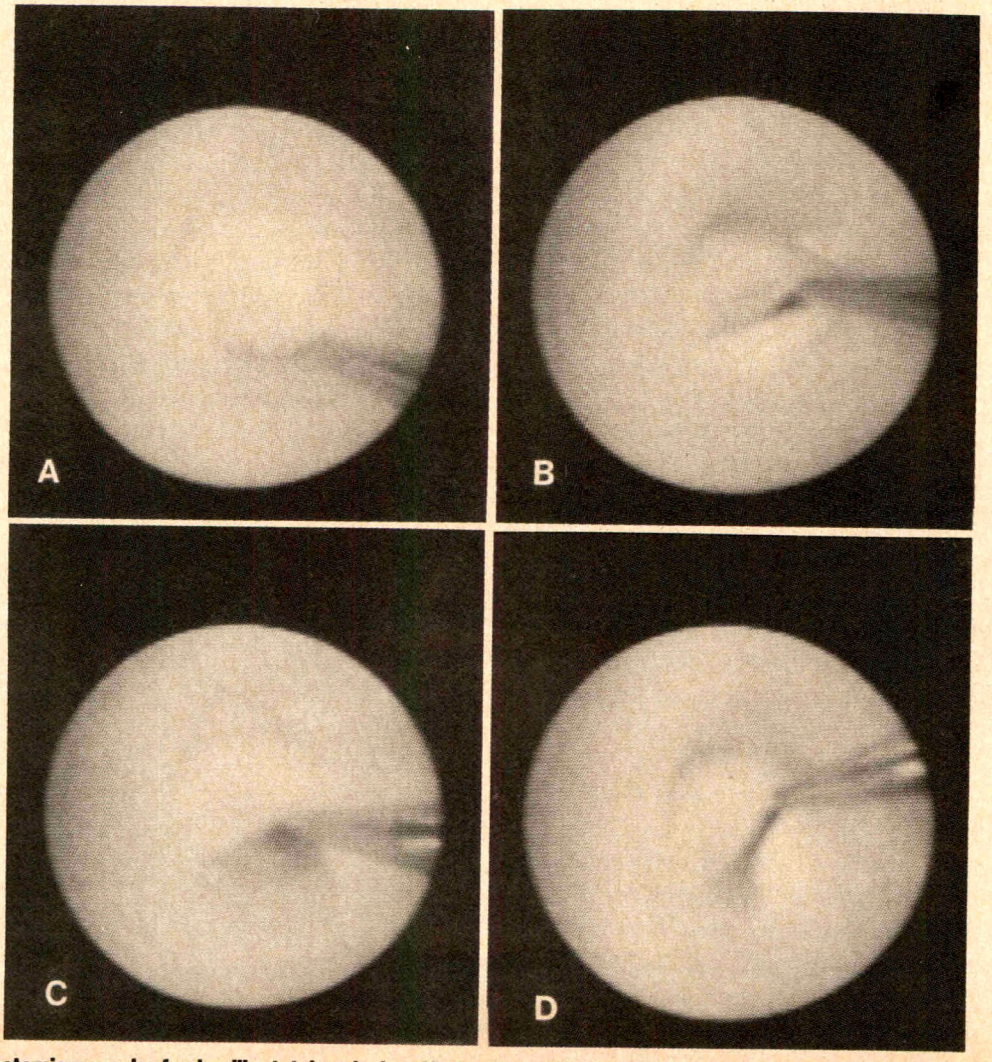


FIGURE 2. Photomicrograph of valve-like total occlusion. Notice the guidewire entering occlusion and lifting up soft plaque *(A to D).*

view in sites proximal to the most distal occlusion were very good because of the lack of blood flow. Withdrawal of the angioscope, which had also worked as a Dotter device, revealed atheromatous structures prolapsed into the vascular lumen (Figure 3).

When no significant residual stenosis remained angiographically, angioscopic visualization of the treated area was performed (Table III). In 10 of 39 sites in which atherectomy with the Simpson device was performed (26%), angioscopy detected a significant amount of residual plaque material. Additional passes of the atherectomy catheter extracted this remaining material. In 5 cases (13%) angioscopy revealed large intimal flaps with the potential to obstruct blood flow. Again, additional passes of the atherectomy device allowed selective removal of these lesions (Figure 4). In 15 of the 39 cases inspected after atherectomy (38%), "tracks" made by the rotating atherectomy blade were found (Figure 5).

TABLE III Angioscopic Findings After Atherectomy (n = 39)

Findings	No.	%
Major plaques	10	26
Major flaps	5	13
Atherectomy "tracks"	15	38
Minor flaps	6	15

DISCUSSION

In this series of 43 patients (57 lesions), we found the adjunctive use of angioscopy to routine angiography safe, quick and effective in evaluating intravascular femoral and popliteal lesions before and after atherectomy. The ability to obtain adequate images was limit-

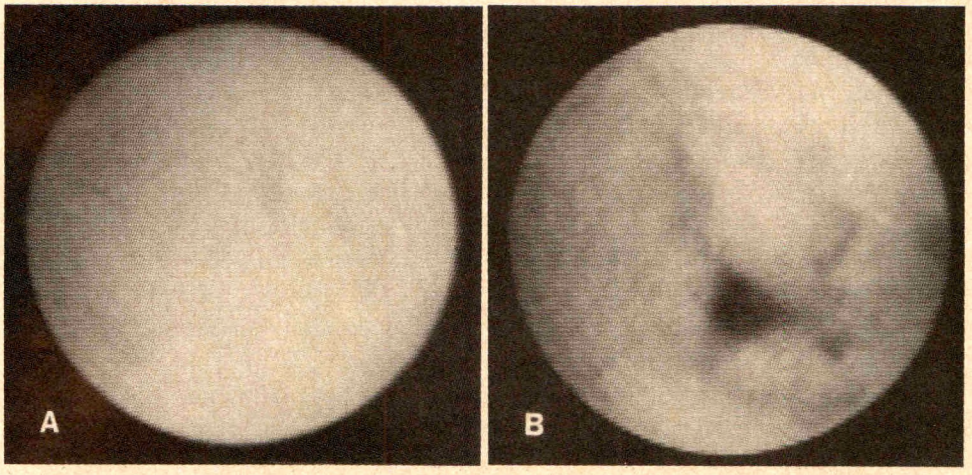


FIGURE 3. Photomicrograph of total occlusion *(A)*. Total occlusion after passage and then withdrawal of angioscope showing recoil of disrupted plaque material *(B)*.

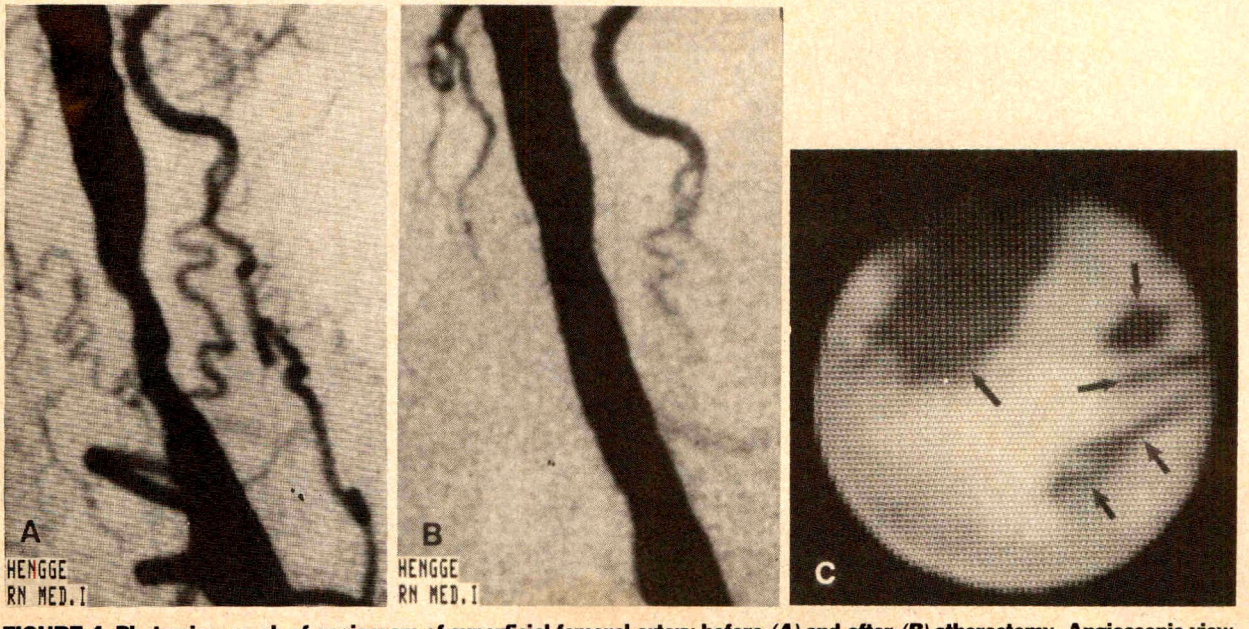


FIGURE 4. Photomicrograph of angiogram of superficial femoral artery before *(A)* and after *(B)* atherectomy. Angioscopic view with large intimal flap in apparent widely patent vessel shown in *B (C)*. Note perforations in intimal flap *(arrows)*.

ed by blood in the field of view due to inadequate saline irrigation and by loss of catheter sterility. Visualization of the target area was excellent: 98% before and 71% after atherectomy, when sterility of the angioscope was maintained. This success rate is comparable to the rate reported by other groups (70 to 95%).[1,11,12]

The role of angioscopy in the management of patients with peripheral vascular disease may be divided into 3 categories.

1. DIAGNOSTIC USE BEFORE INTERVENTION: By transmitting a colorful, magnified sterioscopic view of the arterial lumen, angioscopy allows differentiation of plaque, thrombus and intimal flaps observed in our patients. This is important in deciding the therapeutic intervention when the options of balloon angioplasty, laser angioplasty, atherectomy, or thrombolysis exist. However, stenosis quantification as well as complete morphologic characterization is unreliable because of the difficulty in coaxially aligning the flexible angioscope. Also, overmagnification of proximal objects results in geometric distortion.

2. THERAPEUTIC USE: Under direct vision, the angioscope was used to cross lesions with luminal diameters less than its own dimension. Total occlusions were also safely crossed although visual guidance was not helpful until the angioscope had traversed the lesion. Passage of the angioscope through the total occlusion created plaque distortion, thus forming a channel through which the atherectomy device could be passed. Fifty-four percent of the total occlusions in our series were crossed in this manner. The angioscope was especially useful in directing further interventional therapy, by allowing selective plaque removal without disturbing the integrity of the intervening vessel wall. Although not seen in our study, passage of the angioscope through high-grade stenosis or total occlusions may cause intimal dissections or vessel perforation, thus precluding further attempts at recanalization.[13,14]

3. DIAGNOSTIC USE AFTER INTERVENTION: After atherectomy, the angioscope was very helpful in guiding further therapy. Evaluation of 39 lesions after atherectomy revealed 15 cases (39%) with a significant amount of residual plaque or flow-limiting intimal flaps, not detected by angiography, which required additional atherectomy.

Others have speculated that in total occlusions, the ease of recanalization was dependent on the nature of the underlying lesion. It was generally believed that lesions easily recanalized were composed mostly of thrombus.[15] Our results suggest that some of these angiographically long lesions could be composed of discrete lesions separated by relatively normal vessel wall without thrombus. Although thrombus may be present early in the course of total occlusion, spontaneous thrombolysis with time, as reported in the coronary circulation,[16] or organization within the plaque, may explain the infrequent occurrence of fresh thrombus in our population. We are aware that pressurized irrigation may have caused thrombus embolization when only single discrete stenoses were present. However, in our cases of total occlusion with multiple discrete stenoses, no or only reduced irrigation was necessary to obtain a sufficient field of view, until the most distal occlusion was crossed returning blood flow to the vascular segment.

It has been questioned whether angioscopy, by directing removal of additional plaque or intimal flaps, may have a role in reducing the incidence of restenosis and acute closure.[17,18] Previously, Simpson et al[19] observed that patients with peripheral vascular disease

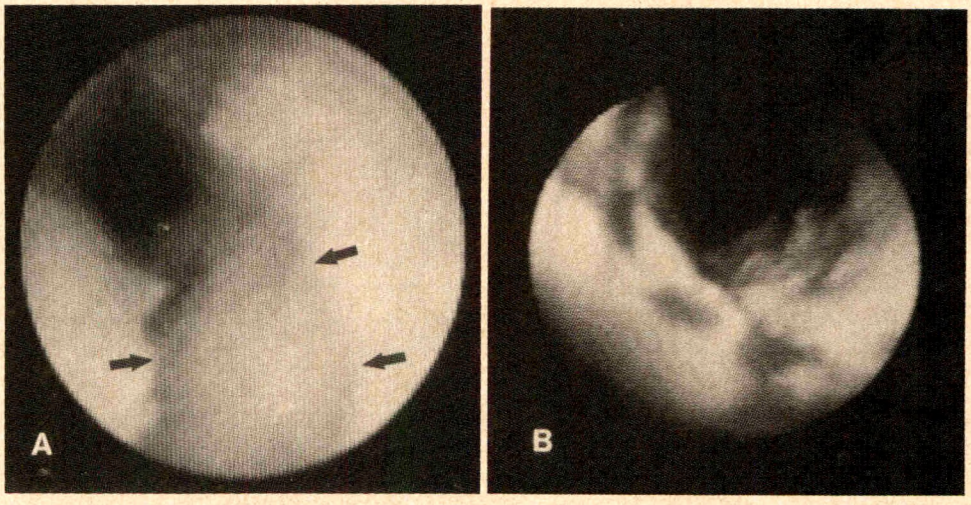


FIGURE 5. Photomicrograph of angioscopic view showing corrugated tracks made by Simpson atherocath after 1 pass with cutter *(A)*. Because of residual plaque, additional passes with atherectomy device yield "reconstructed" vessel *(B)*.

who developed restenosis after atherectomy had lucencies or shadows, without significant recognizable luminal narrowing, on their immediate postatherectomy angiogram. They also showed that a postatherectomy stenosis >30% resulted in a restenosis rate >50% at 6 months. Lesions with residual stenosis <30% had a restenosis rate of 18%. We believe that the use of the angioscope to direct the removal of a maximal amount of tissue may be important in decreasing the restenosis rate. However, long-term studies using the angioscope as a guidance device are needed in order to demonstrate the benefit of this technology in such an application. We also consider it prudent to remove large intimal flaps in an attempt to lessen the incidence of acute closure. This also requires further evaluation.

Two-dimensional intravascular ultrasound has also been shown to detect residual plaque not shown by routine angiography.[20,21] Intravascular ultrasound may be complementary to angioscopy in evaluating intravascular pathology.[22] Whereas the angioscope is excellent for imaging intraluminal detail such as plaque rupture and thrombus, it cannot clearly determine the depth of the intraluminal plaque or the thickness of the vessel wall. This may be especially important in evaluating atherectomy and laser therapy in the coronary artery where the vessel walls are thinner than in the peripheral circulation. Although both devices may detect the presence of intimal flaps,[23–26] since the present side-viewing ultrasound probe lies within the lesion at the time of imaging, it may "stent-up" large flow-obstructing flaps. Future forward-viewing ultrasound devices may avoid this drawback by remaining proximal to the lesion, as does the angioscope, thereby avoiding distortion of the vascular pathology.

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Evolution of Heart Rate Responsiveness After Orthotopic Cardiac Transplantation

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Although anatomic reinnervation of the donor heart is unlikely after transplantation, individual subjects have been noted to show near physiologic heart rate (HR) responses to exercise. To assess development of this phenomenon, we studied HR changes in response to orthostasis and treadmill exercise in 52 orthotopic cardiac transplant recipients grouped according to time after transplantation. In group 1 (2.0 ± 0.9 months), no significant increase in HR was seen up to 100 cardiac cycles after standing. A maximal acceleration of 4.0 ± 3.8 beats was seen within 100 cardiac cycles after standing in group 2 (15.8 ± 5.6 months). Patients in group 3 (42.4 ± 12.4 months) showed significant cardioacceleration by 5 cardiac cycles after standing to a maximum of 10.7 ± 5.8 beats/min within the first 100 cardiac cycles. During exercise, HR increased more rapidly during the first minute in group 3 compared with group 1 ($p < 0.01$). After exercise, HR continued to increase in group 1 but decreased rapidly in the other groups, most notably group 3 (−26.5 ± 16.5 by 2 minutes, $p < 0.0001$ vs groups 1 and 2). These data indicate development of functional reinnervation after orthotopic heart transplantation. The phenomenon of early acceleration of the HR after orthostasis and rapid deceleration after exercise in transplant recipients implies a local cardiac mechanism rather than response to circulating catecholamines.

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There is no evidence that anatomic reinnervation occurs in the human transplanted heart, yet observations in individual patients remote from transplantation suggest that the heart rate (HR) response to certain stresses begins to return to normal.[1] Recent reports indicate that respiratory sinus arrhythmia can be detected after cardiac transplantation[2,3] and we have previously observed a time-dependant normalization of HR responses during exercise.[4,5] To further characterize the development of apparent functional reinnervation of the transplanted heart, HR responses to a change in posture and upright exercise were studied in 52 heart transplant recipients.

METHODS

Study subjects: Forty-six male and 6 female heart transplant recipients were categorized according to time after transplantation (Table I). Group 1 patients (n = 14) were studied early, at 2.0 ± 0.9 months (range 1 to 4) after transplantation. Group 2 patients (n = 20) were studied 15.8 ± 5.6 months (range 12 to 24) after transplantation. Group 3, long-term survivors (n = 18), were studied 42.4 ± 12.4 months (range 33 to 83) after transplantation. Recipient mean age at the time of study was 48 ± 13 years (range 10 to 67). Donor mean age was 25 ± 10 years (range 7 to 53). HR changes in response to standing were compared with a group of 13 untrained healthy volunteers (mean age 25 ± 7 years, range 11 to 36).

Immunosuppressive therapy, the details of which are described elsewhere,[1] consisted of cyclosporine and prednisone in all patients. Azathioprine was added selectively in approximately 50% of patients. At the time of the study, 67% of patients were being treated with antihypertensive medications consisting of a diuretic or a vasodilator, or both. No patients under study were being treated with digitalis, β blockers or verapamil.

Heart rate monitoring: Observations were taken at the time of routine follow-up treadmill exercise testing. Subjects laid quietly for ≥10 minutes. Continuous electrocardiographic recording began during the last minute of rest at a paper speed of 25 mm/s. During continuous recording, the study subjects stood and remained standing for at least 100 cardiac cycles. Ten consecutive cardiac cycles in the supine position immediately before

TABLE I Transplant Recipient Characteristics Related to Time After Transplantation

	Groups			
	1	2	3	ANOVA
No. of patients	14	20	18	
Time after TP (mos)	2 ± 1	16 ± 6	42 ± 12	
Recipient age	44 ± 15	51 ± 11	49 ± 13	NS
Donor age	22 ± 10	28 ± 11	25 ± 8	NS
Ischemic time (min)	232 ± 68	245 ± 88	186 ± 71	NS
Rest BP				
Systolic	135 ± 13	131 ± 15	135 ± 15	NS
Diastolic	80 ± 9	86 ± 8	87 ± 8*	0.05
Rest HR	95 ± 14	93 ± 19	95 ± 12	NS
Max Δ HR standing	+1 ± 1	+4 ± 4	+11 ± 6†	0.0001
Ex. duration (min)	7.4 ± 2.1	9.2 ± 1.9	11.0 ± 3.8*	0.002
Peak ex. HR	128 ± 22	144 ± 17	161 ± 18†	0.0001
Δ HR 2 min post ex.	2 ± 7	−8 ± 13	−27 ± 17†	0.0001

*$p < 0.05$ vs group 1; †$p < 0.05$ vs groups 1 and 2.
Values are expressed as mean ± 1 standard deviation.
ANOVA = analysis of variance; BP = blood pressure; Ex. = exercise; HR = heart rate; Max = maximal; NS = not significant; TP = transplantation.

standing were used to calculate the average RR interval before standing. The response on standing was evaluated by calculating the average RR interval of consecutive groups of 5 of the first 100 cardiac cycles after standing. In the transplant recipients, symptom-limited treadmill exercise was then performed using the Bruce Protocol. HR was recorded at each minute during exercise, at peak exercise, and at each minute up to 6 minutes into the recovery phase.

Statistical analysis: Comparison between the subgroups of transplant patients and normal volunteers was performed using 2-tailed unpaired *t* testing or factorial analysis of variance and Scheffé's test for multiple comparisons.[6] Correlations between continuous variables were assessed by linear regression analysis. Changes in RR interval from baseline were assessed within each group by the paired, 2-tailed *t* test. A p value <0.05 was considered significant.

RESULTS

Resting heart rate: Resting HR in normal volunteers (68 ± 13) was significantly lower than among transplant recipients (94 ± 15, $p < 0.0001$). The resting transplanted HR showed no correlation with the time elapsed since transplantation but did correlate modestly with the donor heart age ($r = 0.46$, $p < 0.0006$). Five transplant recipients (9.6%) had a resting HR <75% of the predicted intrinsic HR calculated using the formula of José et al,[7] intrinsic HR = 118.1 − (0.57 × donor heart age).

Orthostatic heart rate response (Figures 1 and 2): HR response to standing in normal subjects was compared with HR in transplant recipients (Figure 1). An orthostatic increase in HR was strongly related to time after transplantation (Figure 2). Group 1 patients (early) had no significant change in HR (range 0 to +2 beats/min) for up to 100 cardiac cycles after standing

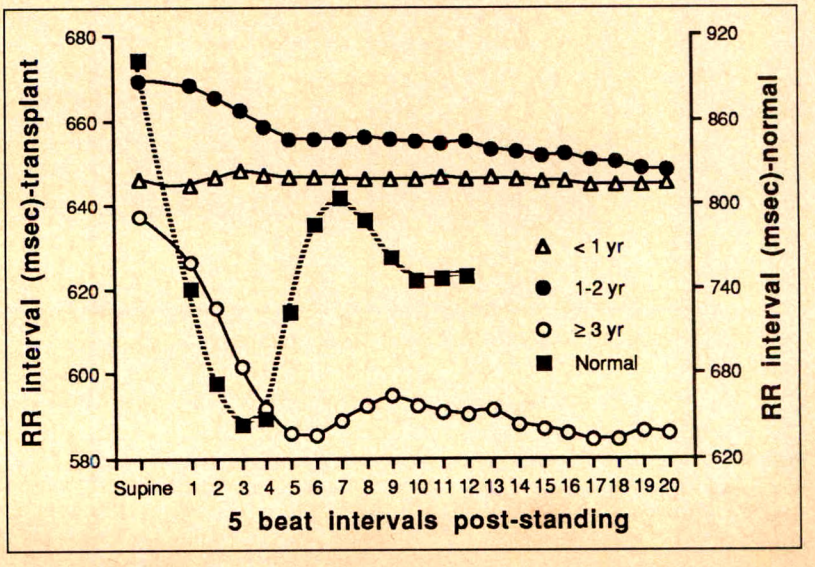


FIGURE 1. Changes in RR interval after standing in normal subjects and heart transplant recipients at varying times after transplantation. Note the different RR interval scale for normal *(right)* and transplant *(left)* subjects.

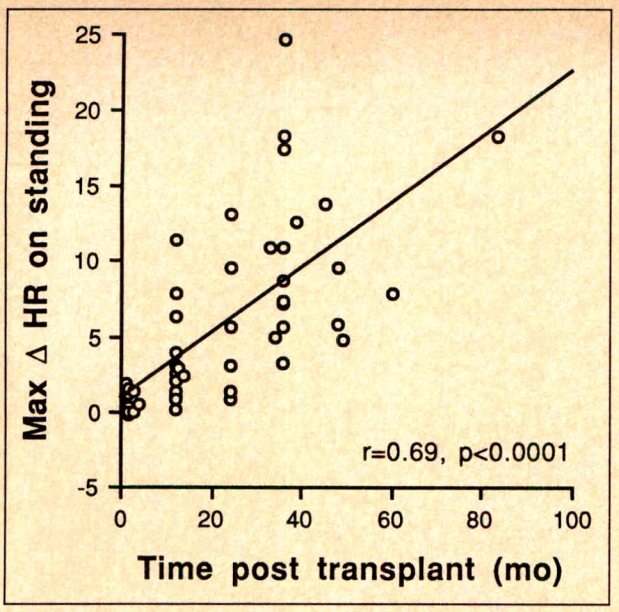


FIGURE 2. Relation of time after (post) transplantation to orthostatic heart rate (HR) response. Max = maximal.

(Figure 1). Group 2 patients (intermediate) had a small but significant ($p < 0.05$) increase in HR by the sixteenth to twentieth cardiac cycle after standing and a maximal increase ranging from 0 to +13 beats/min (mean 4.0 ± 3.8) within the first 100 cardiac cycles. Strikingly, group 3 patients (late) were found to have significant shortening ($p < 0.002$) of the RR interval by the fifth cardiac cycle after standing. In this group, the minimal RR interval was recorded at the twenty-sixth to thirtieth cardiac cycles after standing. In group 3, the maximal increase in HR ranged from +3 to +25 beats/min (mean 10.7 ± 5.8). Among all patients, 21 of 52 had a maximal HR increase of ≥5 beats/min: 0 of 14 in group 1, 6 of 20 in group 2, and 15 of 18 in group 3. In group 3, 8 of 18 had a maximal HR increase of ≥10 beats/min. By multiple linear regression analysis, the time elapsed since cardiac transplantation was the only variable significantly associated with the extent of change in HR on standing. This correlation was significant within the first 10 cardiac cycles after standing and remained highly significant throughout the first 100.

Heart rate response during and after exercise (Figures 3 and 4): The exercise tolerance of patients in group 3 (11.0 ± 3.8 minutes) was significantly higher ($p < 0.005$) than those in group 1 (7.4 ± 2.1 minutes). In contrast to the significantly different responses to standing, the rate of change of HR was comparable among the 3 groups during the first 2 stages of exercise (Figure 3). However, during the first minute of exercise, cardioacceleration was greater in group 3 patients (+5.3 ± 3.9 beats/min) than in group 1 patients (+1.9 ± 1.9 beats/min, $p < 0.01$). By multiple regression analysis, the only variable significantly associated with maximal HR acceleration was the duration of exercise ($r = 0.76$, $p < 0.0001$). Marked differences in HR recovery of the 3 groups were seen early after exercise (Figure 3). Among group 1 patients, HR continued to increase for up to 2 minutes after exercise, whereas almost immediate deceleration was seen in group 2 and 3 patients. At 2 minutes after exercise, 17 of 52 patients had a decrease in HR of ≥15 beats/min: 0 of 14 in group 1, 5 of 20 in group 2 and 12 of 18 in group 3. In Group 3, 7 of 18 had a HR decline of ≥30 beats/min. HR deceleration 1 minute after exercise was related to the time after transplantation, the duration of exercise, and also to the peak HR achieved dur-

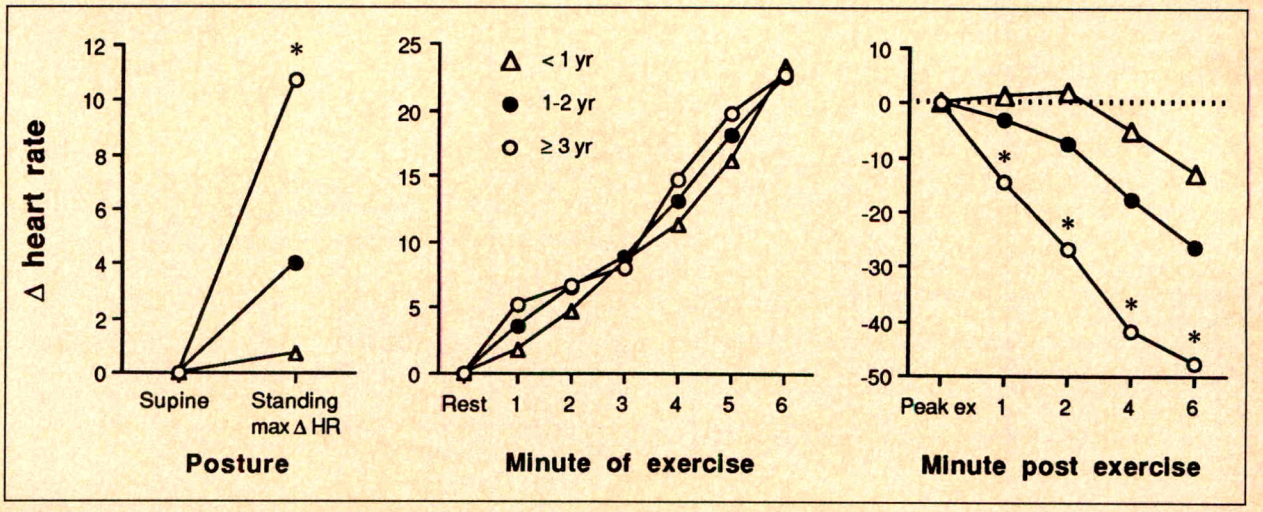


FIGURE 3. Heart rate (HR) responses on standing *(left)*, during early exercise *(middle)* and after (post) exercise *(right)* in heart transplant recipients at varying times after transplantation. *p <0.05 vs <1 year; †p <0.05 vs <1 and 1 to 2 years. ex = exercise; max = maximal.

ing exercise. However, by multiple regression analysis, only the time after transplantation retained significance. The same factors were associated with HR deceleration throughout the recovery phase after exercise. At 6 minutes after exercise, both time after transplantation and peak HR during exercise were independently and significantly associated with the extent of HR deceleration. There was also a close correlation ($r = 0.86$, $p < 0.0001$) between HR response on standing and deceleration after exercise (Figure 4).

DISCUSSION

HR changes in response to standing have been well characterized in normal subjects by Ewing et al[8] and are in agreement with the findings in this study. Typically, HR increases almost immediately, with maximal acceleration around the fifteenth cardiac cycle after standing, followed a rebound slowing, which is most pronounced around the thirtieth cardiac cycle. The mechanism of the initial orthostatic HR response has been further delineated by Borst et al[9] who isolated 2 components within the acceleration phase, an early "muscular reflex" peaking around the third second poststanding and a "baroreceptor reflex" with maximal acceleration around the twelfth second poststanding.

Immediate orthostatic HR changes have not previously been documented in heart transplant recipients. Compared with the normal response, however, the onset of cardioacceleration is delayed and the extent of acceleration is about one-third that of normal. After exercise, Yusuf et al[10] reported that an increase in HR was characteristic of patients early after transplantation, attributed to increased sensitivity of the heart to circulating catecholamines. In the present study, there is again evidence for evolution of this response so that HR late after transplantation, may decline up to 33 beats in the first minute of rest.

Mechanisms of functional reinnervation: The current observations indicate that HR autoregulation develops with time after orthotopic cardiac transplantation. Although we have no evidence to the contrary, anatomic reinnervation (partial or otherwise) is unlikely. Studies on biopsy specimens of hearts taken late after transplantation have not disclosed any histologic evidence of reinnervation.[11] The resting tachycardia, correlation with the calculated intrinsic HR, and blunted HR response to exercise of these patients provide indirect evidence for cardiac denervation.

Altered adrenoreceptor density or increased sensitivity to circulating catecholamines, or both, may also be responsible, although Denniss et al[12] showed that β-receptor density is not significantly different from normal in the transplanted heart. Quigg et al[13] further showed normal sensitivity of the sinus node to β-adrenergic stimulation with isoproteronol. An interesting observation by this group was increased norepinephrine release during exercise in patients late after transplantation compared with normal subjects. This and other studies[14,15] provide evidence that circulating catecholamines play a primary role in HR acceleration during physical exercise after heart transplantation. Catecholamine levels have been reported to increase sharply on standing, within 2 to 5 minutes.[16] Although catecholamine determinations were not done in this study, our finding of significant acceleration within the first 10 cardiac cycles after standing cannot be explained by this effect. Similarly, catecholamine levels have previously been shown to continue to increase after exercise,[17] an explanation for observations of postexercise HR changes early after transplantation but at odds with our observations late after transplantation.

An alternate explanation for this phenomenon may be the emergence of a local mechanoreceptor response via intracardiac feedback. A number of animal experiments[18,19] have demonstrated that cardiac stretch receptors modulate HR, and Hashimoto et al[20] reported a reciprocal relation between sinus node arterial pressure and HR, unaffected by cardiac denervation. Although the bulk of evidence indicates that increasing pressure in the atria elicits a positive chronotropic response,[18] there are also data to suggest that the range of pressure changes and the initial HR influence the direction of HR changes.[18,19] These observations may explain our finding of HR acceleration on standing and

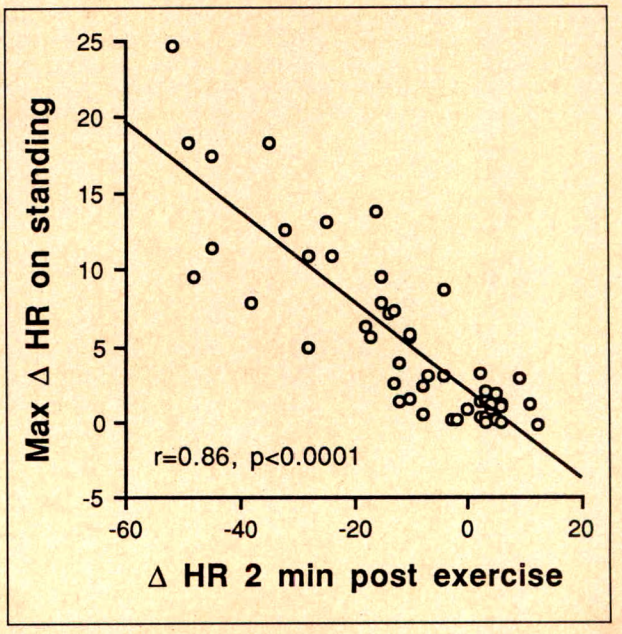


FIGURE 4. Relation of orthostatic heart rate (HR) response and HR recovery after (post) exercise. Max = maximal.

deceleration after exercise, both in the setting of decreasing intracardiac pressures.[1]

There is a marked similarity between the orthostatic HR response in subjects after double autonomic blockade with atropine and propranolol (pharmacologic denervation) and that of our patients late after transplantation, again supporting intrinsic cardiac responsiveness.[8] Kamath et al[2] and Bernardi et al[3] recently reported on the development of limited sinus arrhythmia in some transplant recipients. Because hormonal changes cannot keep pace with respiration, these findings also support cardiac autoregulation of HR. The absence of responsiveness early after transplantation may be secondary to prolonged recovery after the ischemic insult of the transplantation process. A high incidence of sinus node dysfunction has been reported after cardiac transplantation, a finding that may explain the variability of the HR responsiveness in group 2 and 3 patients (Figure 2).

The evolution of HR responsiveness should be kept in mind when conducting studies relating to cardiac physiology in cardiac transplant recipients. Because the use of group statistics in patients at varying times after transplantation may mask distinctive physiologic phenomena, the current data argue that only patient groups homogeneous with respect to time after transplantation be considered for such studies.

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Preserved Atrial Natriuretic Peptide Secretory Function After Cardiac Transplantation

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The purpose of this investigation was to determine whether atrial natriuretic peptide (ANP) secretory function is preserved after cardiac transplantation. Thirteen hemodynamically stable outpatients performed supine exercise on a bicycle an average of 7 months after orthotopic cardiac transplantation. Right atrial pressure increased 2.2-fold (6 ± 1 to 13 ± 2 mm Hg) and pulmonary artery wedge pressure 2.1-fold (11 ± 1 to 23 ± 7 mm Hg) with exercise in the transplant recipients. Resting venous ANP level (114 ± 19 pg/ml) and peak exercise venous level (373 ± 61 pg/ml) was elevated in transplant recipients ($p < 0.001$) compared with control subjects (21 ± 1 and 92 ± 14 pg/ml, respectively. This represents a 3.3-fold (114 ± 19 to 373 ± 61 pg/ml) increase in the ANP level from resting to exercise in transplant recipients and a 4.4-fold (21 ± 1 to 92 ± 14 pg/ml) increase in control subjects. A correlation between venous ANP levels and hemodynamics (right atrial pressure) was observed $r = 0.49$ $p = 0.01$. It is concluded that ANP levels at rest are elevated after cardiac transplant, the levels correlate with the intracardiac hemodynamics, and exercise-induced augmentation of plasma levels occurs.

(Am J Cardiol 1991;68:237–241)

Atrial natriuretic peptide (ANP) plasma levels increase in response to a variety of physiologic stimuli in normal persons and in patients with cardiovascular disease.[1–7] Plasma levels of ANP are elevated in patients with congestive heart failure and there is a correlation between ANP and intracardiac hemodynamics including right atrial, pulmonary artery and pulmonary artery wedge pressures.[8–11]

Magovern et al[12] observed that recipients of orthotopic heart transplants have elevated basal ANP levels compared with patients with coronary disease. Venous ANP levels increase in cardiac transplant recipients in response to dynamic exercise; however, previous studies have not examined the relation between hemodynamics and ANP release.[13,14] Marked increases in pulmonary artery wedge pressure occur with exercise in cardiac transplant recipients with normal baseline hemodynamics with treated cyclosporine.[15,16] Since pulmonary artery wedge pressure has been shown to correlate with ANP levels, and pulmonary artery wedge pressure increases significantly with exercise in cardiac transplant recipients, we hypothesized that exercise would be an excellent provocative physiologic stimulus (increased atrial pressure and wall tension). This investigation determined whether the responsiveness of ANP secretion to exercise was preserved and established a relation between hemodynamics and ANP release in cardiac transplant recipients.

METHODS

Orthotopic cardiac transplantation was performed using standard surgical techniques.[17] Stable outpatient cardiac transplant recipients were enrolled at the time of a surveillance endomyocardial biopsy. Demographics of the study population are listed in Table I. All cardiac transplant recipients were receiving cyclosporine, azathioprine and prednisone immunosuppression and performed supine bicycle exercise in the nonsedated postabsorptive state. All medications except for immunosuppressants were witheld for 12 hours before the study. Symptom-limited supine bicycle exercise was performed in 3-minute stages beginning at a work load of 25 W, with increasing increments of 25 W every 3 minutes as tolerated. Four or more endomyocardial specimens were obtained for histologic analysis and graded using the Billingham criteria.[17] A triple-lumen

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TABLE I Demographics and Hemodynamic Data

Pt. No.	Age (yr) & Sex	Etiology	Days After Transplant	BUN (mg/dl)	Cr (mg/dl)	HR (beats/min)		MAP (mm Hg)		Mean RA (mm Hg)		Mean PA (mm Hg)		PAW (mm Hg)		CI (liters/min/m²)		SVI (ml/min/m²)		SVR (dynes · sec · cm⁻⁵)		PVR (dynes · sec · cm⁻⁵)		Ex. Time (sec)
						Base	Peak	Base	Peak	Base	Peak	Base	Peak	Base	Peak	Base	Peak	Base	Peak	Base	Peak	Base	Peak	
1	49 M	CAD	24	27	1.4	97	143	131	108	8	29	16	33	8	20	3.8	6.0	39	42	1,407	726	172	222	744
2	51 M	DC	33	25	1.2	92	120	93	101	5	11	15	30	8	18	2.6	6.8	29	56	1,506	636	243	189	780
3	33 M	DC	35	25	1	75	114	113	114	9	16	26	40	16	32	2.2	4.7	30	42	1,797	852	414	299	810
4	53 F	DC	72	25	0.9	89	113	104	103	6	10	17	22	8	14	2.6	4.8	29	43	2,080	1,111	340	237	660
5	38 M	DC	84	26	1	94	120	123	123	5	13	24	48	16	32	2.6	4.4	29	37	1,659	1,135	324	443	622
6	45 M	DC	96	11	1.2	100	134	111	115	10	18	27	40	15	25	4.2	6.8	42	50	1,011	648	246	225	630
7	29 M	Myocarditis	111	36	1.5	83	127	127	127	9	18	30	55	15	38	2.9	6.2	35	49	1,666	776	393	336	800
8	31 F	Myocarditis	255	29	1.5	86	120	112	103	2	10	10	27	5	16	3.8	9.1	45	76	1,314	509	117	133	750
9	39 M	CAD	272	35	1.3	91	120	128	131	3	12	14	32	7	20	3.4	9.9	38	83	1,583	561	173	137	821
10	46 M	CAD	276	35	1.6	97	150	117	153	6	11	15	36	8	25	2.0	6.1	21	41	2,057	893	264	210	885
11	55 F	CAD	381	17	0.9	81	141	108	128	4	5	16	34	12	18	2.5	5.4	30	38	2,286	1,231	387	327	740
12	45 F	DC	486	39	1.3	92	126	119	126	4	11	18	36	10	20	1.8	4.5	20	36	2,532	1,069	383	305	470
13	50 M	CAD	563	22	1.4	98	120	113	115	4	7	17	27	10	16	3.3	7.3	34	62	1,522	697	229	164	1,320
Mean ± SEM	44 ± 2	Base	207 ± 50	27 ± 2	1.3 ± 0.07	90 ± 2		115 ± 3		6 ± 1		19 ± 2		11 ± 1		2.9 ± 2		32 ± 2		1,724 ± 116		284 ± 27		771 ± 55
*p < 0.05		Peak				127 ± 3*		119 ± 4		13 ± 2*		35 ± 3*		23 ± 2*		6.3 ± 5*		50 ± 4*		834 ± 66*		248 ± 25		

BUN = blood urea nitrogen; CAD = coronary artery disease; CI = cardiac index; Cr = creatinine; DC = dilated cardiomyopathy; HR = heart rate; Ex. = exercise; MAP = mean arterial pressure; PA = pulmonary artery; PAW = pulmonary artery wedge; PVR = pulmonary vascular resistance; RA = right atrial; SVI = stroke volume index; SVR = systemic vascular resistance; SEM = standard error of the mean.

thermodilution pulmonary artery catheter was inserted to measure resting and peak exercise right-sided heart pressures. Thermodilution cardiac outputs were obtained in triplicate with <10% variability. Blood samples for ANP assay were obtained at rest and peak exercise from the superior vena cava, right atrium, right ventricle and pulmonary artery while the patient was supine with the feet upright.

The control group consisted of 13 female volunteers (mean age ± standard deviation 25 ± 2 years) who were enrolled in a study evaluating the influence of exercise on sex hormones.[18] These women were considered "athletic" based on having run a minimum of 25 miles/week for ≥12 months before the study. Exercise was performed on a Quinton model 884 Uniwork upright bicycle ergometer beginning at a work load of 33 W and increasing by 33 W every 3 minutes until the subject could not continue any further due to exhaustion. Blood samples for ANP assay were obtained from a peripheral vein at rest and every 8 minutes during the exercise period. The control subjects achieved a maximal heart rate >160 beats/min with exercise, and the time required to reach exhaustion was 21 ± 1 minutes. Intracardiac pressures were not obtained in the control population. Venous ANP levels (superior vena cava or peripheral vein) were used for comparisons between the control and study population. The protocol was approved by the Human Subjects Review Committee and all subjects gave informed consent.

The ANP levels were determined by a modification of the α-human ANP radioimmunoassay kit produced by Peninsula Laboratories. The sensitivity of the assay in our laboratory is 20 pg/ml of plasma. The intra- and interassay coefficients of variation for this radioimmunoassay were 4 and 22%, respectively. The values were calculated using control-spiked samples of plasma previously stripped with charcoal and assayed at 3 separate known concentrations on the standard curve. Unextracted charcoal-treated plasma was added to the assay curve and all plasma samples were assayed with nonspecific (e.g., no ANP antibody added) tubes to correct for further nonspecific protein binding.

Statistics: Measurements are expressed as mean values, with the standard error of the mean as the index of dispersion. The unpaired Student's *t* test was used to compare the resting ANP levels in the normal and transplant patient groups. Analysis of variance was performed on the ANP levels obtained from different intravascular sample sites. Rest and peak exercise ANP levels among matched patient groups were compared using the paired Student's *t* test. Simple linear regression was used to determine the relation between the ANP level and hemodynamic measures. Results were considered significant at $p < 0.05$.

RESULTS

Demographic and hemodynamic data (Table I): Demographics, baseline and peak exercise hemodynamic findings are listed in Table I. All patients exercised until exhaustion and the mean work load was 44 ± 6 W. Endomyocardial biopsy specimens demonstrated that 12 of the 13 patients did not have rejection that required treatment. One patient had mild rejection and was treated. Twelve of the 13 patients had no fibrosis or focal areas considered to represent old biopsy sites, and 1 patient had patchy interstitial fibrosis.

Resting atrial natriuretic peptide levels in cardiac transplant recipients (Figure 1): The mean resting ANP levels were superior vena cava 114 ± 19 pg/ml, right atrium 165 ± 33 pg/ml, right ventricle 130 ± 20 pg/ml and pulmonary artery 134 ± 20 pg/ml. An upward trend in ANP was seen from the superior vena cava to the right atrium. However, no significant difference in the levels were present when analyzed with analysis of variance. The baseline venous level (114 ± 19) was significantly elevated in transplant recipients ($p < 0.001$) compared with levels in control subjects (21 ± 1).

Exercise atrial natriuretic peptide levels in cardiac transplant recipients (Figures 1 and 2): There was a marked and consistent increase in ANP levels during exercise at all 4 sampling sites compared with levels during rest in cardiac transplant recipients. The exercise values were superior vena cava 373 ± 61 pg/ml, right atrium 472 ± 59 pg/ml, right ventricle 422 ± 60 pg/ml and pulmonary artery 412 ± 60 pg/ml. Analysis of variance demonstrated no significant intracardiac variability in the ANP levels sampled at peak exercise.

Exercise venous ANP level (373 ± 61) was significantly elevated in transplant recipients ($p < .001$) compared with levels in the control group (92 ± 14) (Figure 2). A 3.3-fold (114 to 373 pg/ml) increase in the ANP level from resting to exercise was observed in transplant recipients. In the control group a 4.4-fold (21–92 pg/ml) increase in the venous ANP level with exercise was demonstrated. In the cardiac transplant recipients, the right atrial mean pressure increased 2.2-fold (6 ± 1 to 13 ± 2 mm Hg) from baseline to peak exercise, while the pulmonary artery wedge pressure increased 2.1-fold (11 ± 1 to 23 ± 7 mm Hg).

Hemodynamic correlations with atrial natriuretic peptide levels: Simple linear regression was performed to determine the relation between hemodynamics and ANP levels. Levels during rest and exercise in the 13 transplant recipients were analyzed with the respective hemodynamics, and the correlations were as follows: superior vena cava ANP and mean right atrial pressure, $r = 0.48$ $p = 0.01$; superior vena cava ANP and mean pulmonary artery wedge pressure, $r = 0.48$ $p = 0.01$; right atrial ANP and mean right atrial pressure, $r = 0.49$ $p = 0.01$; right atrial ANP and mean pulmonary artery wedge pressure, $r = 0.51$ $p = 0.008$; right ventricular ANP and mean right atrial pressure, $r = 0.56$ $p = 0.003$; right ventricular ANP and mean pulmonary artery wedge pressure, $r = 0.54$ $p = 0.004$.

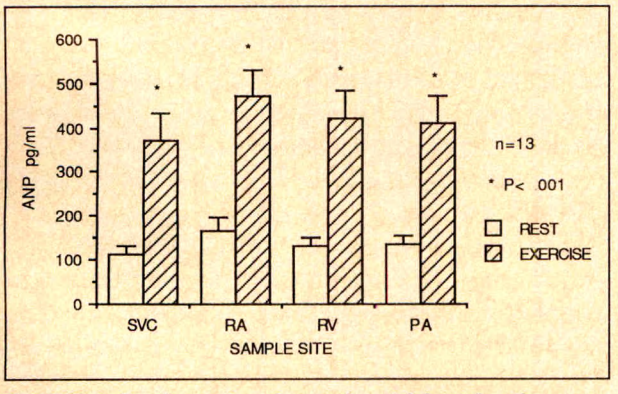


FIGURE 1. Resting and peak exercise atrial natriuretic peptide (ANP) levels in cardiac transplant recipients. There is a significant increase in the level from each sample site when comparing resting and exercise values ($p < 0.001$). All values are mean ± standard error of the mean. PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

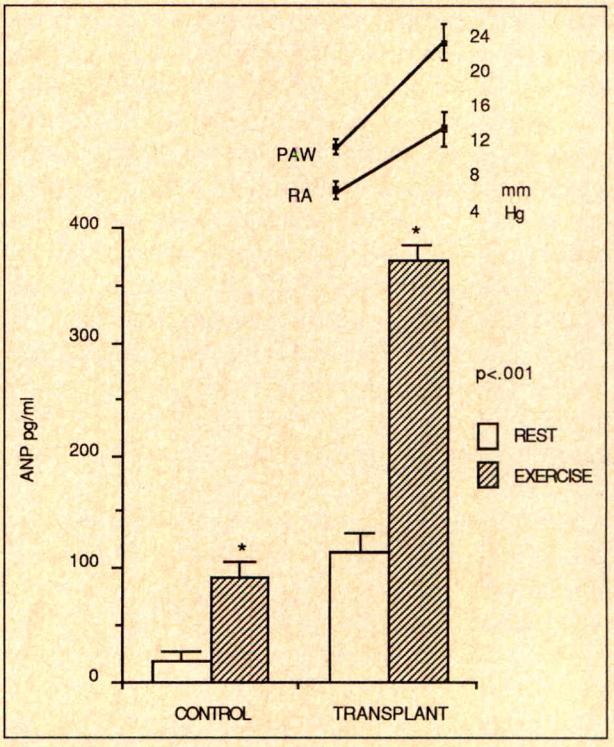


FIGURE 2. Resting and peak exercise venous atrial natriuretic peptide (ANP) levels are shown in normal subjects (CONTROL) and cardiac transplant recipients (TRANSPLANT). *Upper right inset,* pulmonary artery wedge (PAW) and right atrial (RA) pressures at rest and during peak exercise from transplant patients are shown. Peak exercise level in transplant group (373 pg/ml) was significantly higher than in control group (92 pg/ml, $p < 0.001$). All values are mean ± standard error of the mean.

DISCUSSION

The cardiac transplant recipients exercised until exhaustion and developed significant increases in the right atrial and pulmonary artery wedge pressures. Simultaneously, a marked increase in the peak exercise venous ANP levels (3.3-fold) was observed. This is similar to the increase reported with exercise in normal subjects ($n = 4$) by Raine et al[8] (3.1-fold [33 to 102 pg/ml]) and the increase observed in our control subjects (4.4-fold [21 to 92 pg/ml]). Despite the elevated resting ANP levels in cardiac transplant recipients, an increase in ANP levels can occur when a provocative stimulus that increases right atrial and pulmonary artery wedge pressures is applied. We chose to sample ANP from multiple cardiac chambers because previous studies have shown the best hemodynamic correlations with right ventricular ANP levels.[19] A relation has been demonstrated in cardiac transplant recipients between intracardiac pressure and ANP levels. We cannot conclude whether superior vena cava, right atrial or right ventricular ANP samples correlate best with hemodynamics because of the lack of significant variability in samples from these sites.

Potential factors related to elevated resting atrial natriuretic peptide levels in cardiac transplant recipients: The cardiac transplant recipients studied were hypertensive (mean arterial pressure 115 ± 3 mm Hg); however, hemodynamics at rest were essentially normal. A relation between resting ANP levels and blood pressure was not found. Therefore no direct etiologic relation was observed between ANP levels, blood pressure or systemic vascular resistance. ANP levels are elevated in subjects with essential hypertension, but the levels previously reported are lower than the resting ANP levels observed in our transplant recipients.[20–22] Impairment of ventricular relaxation may contribute to ANP secretion by increasing left atrial afterload.[22] The transplanted heart is noncompliant,[15,16] and perhaps the striking increase in pulmonary artery wedge pressure with exercise in transplant patients (with normal systolic function) indicates an abnormality of diastolic function. These factors may contribute to impairment of ventricular relaxation, which may basally stimulate ANP release.

Renal function (glomerular filtration rate) and age are related to ANP levels.[23] No correlation between ANP levels and serum creatinine or age was demonstrated in the transplant recipients. All patients were receiving cyclosporine, which promotes renal tubular secretion of creatinine; thus, the serum creatinine and creatinine clearance underestimate the true glomerular filtration rate.[24] Cyclosporine impairs natriuresis in renal transplant recipients[25]; thus "cyclosporine related" sodium retention may serve as a stimulus for ANP release. The measurement of ANP levels in orthotopic cardiac transplant recipients not receiving cyclosporine would help to clarify these issues.

Anatomically, the explanation may be a function of the ubiquitous biatrial enlargement and attendant wall stretch that occurs when the donor recipient anastomosis is created surgically at the time of transplantation. Roman et al[26] recently reported that marked left atrial dilatation (distension) is a potent stimulus to ANP release. Although right atrial and pulmonary artery wedge pressures at rest remain normal, mechanically induced atrial enlargement and stretch may serve as a chronic stimulus (increased wall tension) to ANP secretion.

Role of cardiac denervation in the control of atrial natriuretic peptide release: Atrial pressure and perhaps more importantly atrial stretch or wall tension may independently govern ANP release. The involvement of the sympathetic nervous system in the release and action of ANP on target organs is poorly understood. Goetz et al[27] showed that dogs completely devoid of cardiac innervation can increase their circulating ANP >400% with atrial distention. Furthermore, despite a 4-fold increase in ANP levels, no associated natriuresis or diuresis was noted. Goetz et al concluded that cardiac innervation was not necessary for release of ANP, but the renal response appeared dependent on cardiac innervation.

This investigation has not determined what contribution to the net ANP level is made by the donor versus the recipient atria. This is a crucial issue because the donor atria are surgically denervated and documentation of ANP release by donor atria would indicate that secretory function is preserved despite sympathetic denervation. Implantation of the total artificial heart leaves the innervated native atria intact. Schwab et al[28] reported ANP levels of 60 and 39 pg/ml in 2 humans implanted with a total artificial heart. Our data in 1 patient who received a total artificial heart is similar.[29] In this person, serial measures of venous ANP were obtained. Immediately before surgery the venous ANP level was 310 pg/ml, the level decreased to 45 pg/ml 24 hours after surgery and <20 pg/ml 5 days after implantation. The levels measured in these persons are much lower than the levels observed after orthotopic transplantation and implies that the denervated donor atria make a contribution to the net ANP level in cardiac transplant recipients.

Study limitations: The control population was younger, entirely female and exercised upright. Our control subjects ("normals") were in fact trained athletes with presumably altered cardiovascular physiology; however,

the ANP exercise response closely approximated the only previously reported values in normal subjects.[8] The marked absolute differences (in ANP levels) between the control subjects and cardiac transplant recipients documents the striking elevation in ANP levels in cardiac transplant recipients at rest and during exercise. The control subjects were sampled upright and the transplant patients, supine. Differences in loading conditions and subsequently atrial pressure between upright and supine posture may have partially contributed to the observed differences in ANP levels between the control and study population.[30] Because of limited patient numbers and lack of rejection episodes, we were unable to determine if ANP levels increase with moderate or severe rejection. Atrial natriuretic peptide levels probably are not a useful marker of mild allograft rejection, which usually is present without associated hemodynamic compromise.

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Ability of High-Intensity Ultrasound to Ablate Human Atherosclerotic Plaques and Minimize Debris Size

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To investigate whether high-intensity ultrasound can destroy atherosclerotic plaques while sparing the normal arterial wall, 279 normal human aortic sites and 119 fibrous and 193 calcified plaques, obtained from 24 necropsies, were insonified in a water tank, at 20 kHz and at 5 different power intensities, ranging from 68 W/cm^2 (P_1) to 150 W/cm^2 (P_5). These intensities were associated with a total excursion of the ultrasound irradiation apparatus tip from 90 to 268 μm, respectively. Time to perforate normal aortic sites and fibrous and calcified plaques was recorded at each intensity. There was no difference in perforation time between normal aortic sites and fibrous and calcified plaques when high-power levels (P_2 to P_5) were used. However, at the lowest power (P_1), perforation time for the normal aortic wall was significantly longer than for fibrous and calcified plaques: 30 ± 18 seconds (166 observations), 14 ± 7 seconds ($p < 0.001$) (78 observations) and 12 ± 8 seconds ($p < 0.001$) (115 observations), respectively. When perforation times for normal vessel wall versus fibrous plaque and normal vessel wall versus calcified plaque from the same necropsy specimen were compared in a pairwise manner, the results were: 29 ± 13 vs 16 ± 7 ($p < 0.001$) (48 paired observations) and 26 ± 9 vs 10 ± 5 seconds ($p < 0.001$) (55 paired observations), respectively. Regardless of whether paired or unpaired comparison was applied, no significant difference was found in perforation time between fibrous and calcified plaques. The debris did not differ in size as measured separately for normal sites and fibrous and calcified plaques by a computer-interfaced Channelizer® and Coulter® Counter system. A total of 57,863 particles were counted and measured. The mean particle diameter was 7.0 ± 5 μm (range 4.8 to 15.8). Thus, ultrasound may selectively ablate human atherosclerotic plaques at power intensities ≤68 W/cm^2.

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Currently accepted angioplasty technology[1–3] is rapidly changing with the introduction of new devices and techniques.[4,5] Two critical issues need to be addressed and resolved in the introduction of new angioplasty methods: plaque selectivity and debris removal. High-intensity ultrasound has been reported effective in atherosclerotic plaque and thrombus dissolution in vitro,[6–9] as well as in the surgical debridement of calcified heart valves.[10] Thus, it was the goal of this study to (1) investigate whether high-intensity ultrasound can discriminate among various kinds of plaques and normal vessel wall, (2) determine the power intensities at which this selectivity occurs, and (3) investigate the size of the resulting debris and histologic damage to aorta specimens.

METHODS

Pathologic specimens: Fresh, unfixed thoracic or abdominal aortic specimens from 24 autopsies were collected within 12 hours of death. The aortas came from 14 women and 10 men, aged 30 to 92 years (mean 69). The aortic specimens were cut to 4 × 6-cm pieces, opened longitudinally and laid flat with the intimal surface facing up. The aortic samples were then suspended between 2 clamps and immersed in saline solution in a water tank. Visual inspection and palpation of the intimal surface was used to characterize gross pathologic changes. Categories defined were normal aorta, fibrous plaque and calcified plaque. Fibrous plaque was defined as a raised, yellow or grayish, rubber-like lesion.

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Calcified plaque was defined as a raised, yellow or grayish lesion, hard on palpation, with visible calcified spots or scales. For more accurate calcium content determination, all specimens were imaged by x-ray using a Faxitron® (Hewlett-Packard, McMinnville, Oregon) at 30 KeV for 45 seconds. After ultrasound irradiation of selected areas, the 1 or 2 most characteristic locations of each type of plaque were marked with india ink according to its initial macroscopic classification. Then, the specimens were fixed in 4% neutral buffered formalin, decalcified with Cal-Ex II (Fisher Scientific), embedded in paraffin and sectioned into 5-μm-thick slices. Approximately 400 sections (10 sections per location) were cut and stained with hematoxylin and eosin, and with the Gomori trichrome connective-tissue method. A blinded microscopic evaluation consisted of (1) confirmation of plaque type, and (2) evaluation of histomorphologic changes produced by ultrasound along the beam path and in adjacent tissues. Occasional minor disagreements with initial macroscopic classification were corrected according to histology and x-ray. This clearly separated fibrous from calcified plaques and precisely characterized the region of holes created by ultrasound irradiation (Figure 1).

Ultrasound exposure: We used a commercially available 20 kHz, high-intensity ultrasound probe (W-375 Sonicator®, Heat Systems, Farmingdale, New York) whose tip was placed perpendicular to the suspended tissue at an approximate pressure of 50 g as indicated by a digital scale placed below the water tank during the whole procedure. Because the specimens were initially precompressed with the probe tip (50 g), the perforation time was easily recordable by simple visual inspection of elastic recoil motion of the specimen toward the probe at the moment when the perforation took place. Besides this visual indication, the sound of surrounding cavitating fluid drastically changed at the moment of perforation from a dampened to a high pitch of unhampered oscillations of the probe tip. In each specimen, 5 to 10 different locations were insonified. Each location contained either normal aortic wall or fibrous or calcified plaques. For each exposure, 1 of 5 different power settings was used. These settings ranged from P_1 to P_5, as indicated on the power generator dial. The ultrasound energy was applied in a continuous mode through a transducer probe with a 2.2-mm diameter titanium alloy tip. The time required for the probe to perforate the entire thickness of the aortic wall from the endothelial to the adventitial side was recorded by stopwatch. The probe pressure against the endothelial surface was kept constant during ultrasound irradiation. None of the insonified plaques was penetrable by simple Dotter maneuver, although such an attempt, sometimes using substantial pressure, was a part of a routine preablation procedure.

Acoustic power output measurement: To estimate the acoustic power output by a calorimetric method, the Sonicator tip was placed in a styrofoam cup filled with 50 g of water, and the water temperature increase was measured during insonification. To reduce air cooling of the water, a plastic lid, with holes cut for the tip and a thermocouple, was used as a cover. The tip was positioned and adjusted to 1 cm below the water surface. A digital thermocouple probe was also immersed and positioned 1 cm from the probe tip. The water temperature was recorded every 30 seconds for a total of 5 minutes at each of the 5 instrument power settings (P_1 to P_5). The temperature increase (T to T_0) was plotted with T_0, defined as the temperature at time t = 0, versus time for each of the 5 power settings. The slope of each curve $\Delta T/\Delta t$ is related to the rate of heating of the water $\Delta Q/\Delta t$ by the equation: $P \cong \Delta Q/\Delta t = Cm\ \Delta T/\Delta t$ where P = power output, m = mass of water in the cup (50 g) and C = 4.19 J/g°C (specific heat of water). The specific heat of the submerged tip was determined to be negligible. The calculated power output was expressed in watts per actual radiating tip surface area (0.038 cm^2) and in an equivalent wattage per cm^2.

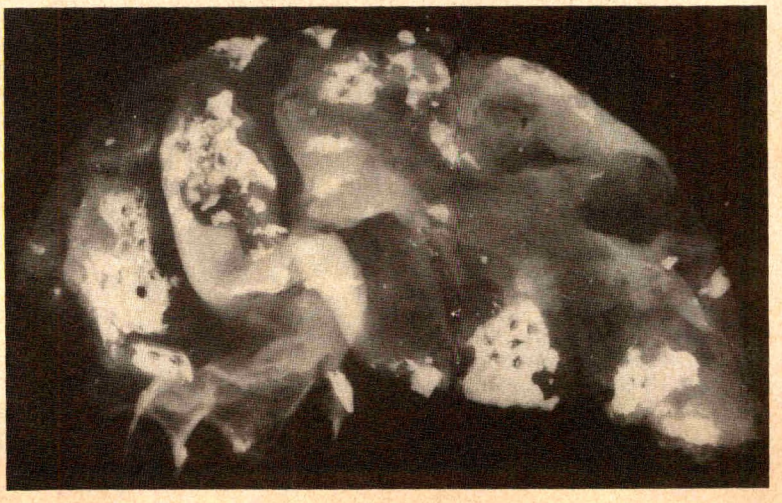


FIGURE 1. X-ray representation of ultrasonically irradiated specimen of human thoracic aorta. Intensely opacified calcified plaques are clearly displayed. Small holes in plaques were created by ultrasonic irradiation and perfectly match the probe tip shape and diameter.

Tip displacement measurement: The magnitude of tip displacement was determined by a mechanical gauge instrument positioned directly against the tip-radiating face. Half-amplitude of longitudinal displacement was directly determined in microns by dial movement on the instrument's scale. An additional method of optical measurement of magnitude of oscillation was performed by placing a probe tip under a microscope at 50× magnification. When energized, the tip displayed a blurring shade over the microscope's built-in metered scale, indicating the total amplitude of longitudinal motion.

Debris size measurement: After ultrasound exposure at the lowest power setting (P_1), the saline solution in the water tank was homogenized by stirring, and 10 ml were withdrawn. This 10 ml was then ultracentrifuged at 25,000 rpm for 20 minutes, the supernatant discarded, and the sediment resuspended in 2 ml of saline. This suspension was analyzed for particle count and size, using model ZBI Coulter Counter and Channelizer® equipment (Coulter Electronics, Hialeah, Florida) interfaced with an Apple® II computer running AccuComp™/C1000 software. Coulter Isoton II® (330 mOsm/l) was used as the electrolyte solution. An aperture diameter of 100 μm was used, with a shape factor of 1.5 for nondeformable spherical particles, and a magnification factor of 2, as previously described.[11] The Counter and Channelizer calibration studies were performed with latex spheres that had a mean volume of 113 femtoliters (fl) (6-μm diameter) (Particle Information Services, Los Altos, California). Particle sizes resulting from exposures of normal aorta, and fibrous and calcified plaques were measured 5 times each. Light microscopic examination of the particles was also performed.

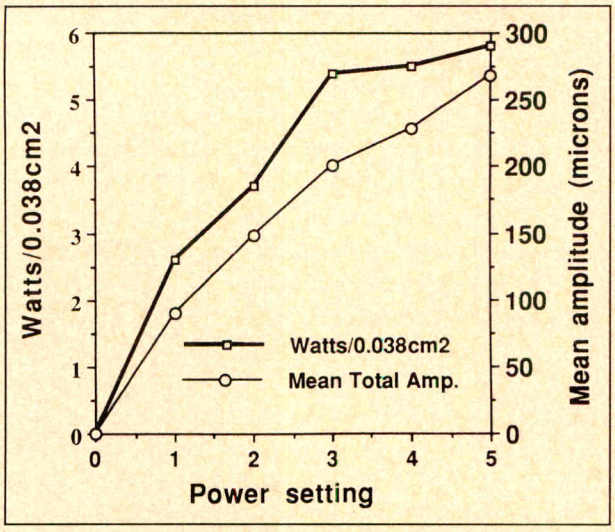


FIGURE 2. Line graph of instrument power settings *(x axis)* versus calorimetrically measured power intensities *(left-hand scale)* and strain gauge measurement of amplitude (Amp.) of ultrasonic probe tip motion *(right-hand scale).*

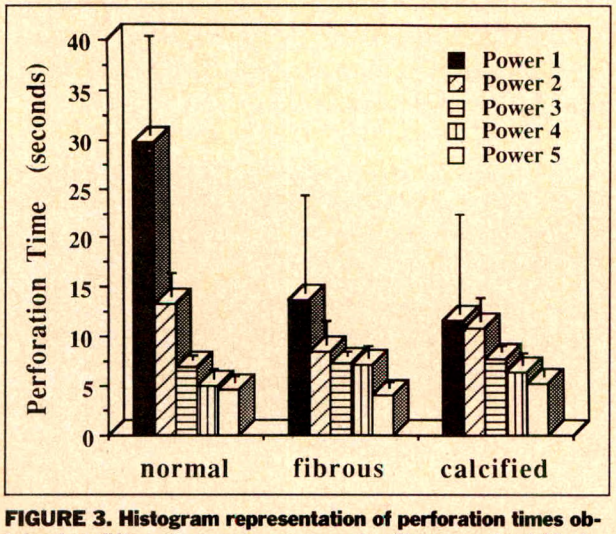


FIGURE 3. Histogram representation of perforation times obtained at different exposure powers for fibrous and calcified plaques, and normal aortic wall. At the lowest setting (Power 1), time to perforate normal aortic wall was significantly longer than time to perforate fibrous ($p < 0.001$) or calcified plaque ($p < 0.001$). *Error bars* refer to standard error.

Statistical analysis: The perforation times at each of the 5 power intensities, and for normal aortic wall and fibrous and calcified plaques, were analyzed and compared using 1-way analysis of variance. Paired Student's *t* tests were used to compare perforation times for adjacent samples of normal aorta and atherosclerotic plaque in the same specimen. Unpaired Student's *t* test was used to compare perforation times among the 3 categories of tissues (normal, and fibrous and calcified plaques). Significance was defined as $p \leq 0.05$. Perforation times were also studied and compared according to 4 patient-age categories: 30 to 40, 55 to 65, 66 to 75 and >75 years. Owing to the small number of patients in each subgroup, nonparametric Mann-Witney U test was used to compare the groups.

RESULTS

Power output and magnitude of tip displacement: The average power output, as determined for each of the 5 power settings, was: P_1, 2.6 W/0.038 cm^2 (effective radiating surface area) or an equivalent of 68 W/cm^2; P_2, 3.7 W/0.038 cm^2 or 97 W/cm^2; P_3, 5.4 W/0.038 cm^2 or 142 W/cm^2; P_4, 5.5 W/0.038 cm^2 or 145 W/cm^2; and P_5, 5.7 W/0.038 cm^2 or 150 W/cm^2 (Figure 2).

The mean tip displacements obtained by the mechanical gauge at each instrument intensity setting were: 90 μm at P_1, 148 μm at P_2, 200 μm at P_3, 228 μm at P_4, and 268 μm at P_5 (Figure 2). Optical measurements using light microscopy yielded similar values that did not differ significantly from readings obtained by the mechanical gauge.

Perforation time analysis: A total of 591 locations were irradiated. This included 279 normal sites and 193 calcified and 119 fibrous plaques. The analysis of perfo-

ration times (Figure 3) in both kinds of plaques and in normal aortas showed an inverse relation between the duration of ultrasound irradiation and the ultrasonic power applied. When analyzed and compared by both unpaired and paired Student's *t* tests, no significant difference was found in perforation times between fibrous and calcified plaques and normal aortic sites at the 4 higher powers (P_2 to P_5). However, at the lowest setting (P_1), time to perforate normal aortic sites was significantly longer than time to perforate fibrous or calcified plaques: 30 ± 18 seconds (166 observations) vs 14 ± 7 seconds ($p < 0.001$) (78 observations) vs 12 ± 8 seconds ($p < 0.001$) (115 observations), respectively (Figure 3). When paired data for exposed normal aortic wall adjacent to fibrous or calcific plaque in the same necropsy specimen were compared, the results were 29 ± 13 vs 16 ± 7 seconds (normal vs fibrous plaque, $p < 0.001$, 48 paired observations) and 26 ± 9 vs 10 ± 5 seconds (normal vs calcified plaque, $p < 0.001$, 55 paired observations). Interestingly, no significant difference was found between time to perforate fibrous plaque and time to perforate calcified plaque. Also, at all power settings, time to perforate normal vessel wall and fibrous and calcified plaques did not differ significantly among the 4 age groups.

Histology: The histologic examination of insonified parts showed the disappearance, physical disintegration and mechanical ablation of underlying tissues. The effect was strictly confined to the exposed area of the vessel, and the created holes matched the shape of the probe tip (Figure 4). No charring or desiccation suggesting thermal injury was present. Also, a majority of exposed normal sites showed some degree of intimal or medial fibrosis, or both, indicating that in the presence of advanced atherosclerosis, the plaque-adjacent, normal-looking areas of aortic wall are not healthy and unaffected by the atherosclerotic disease. Microscopic examination of the debris particles revealed calcium

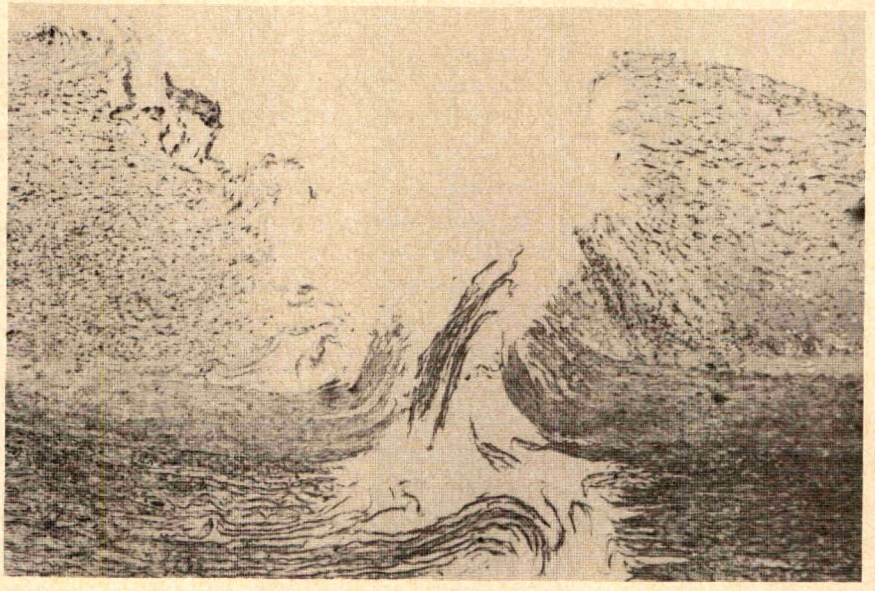


FIGURE 4. Photomicrograph of human fibrous atherosclerotic plaque in a specimen of thoracic aorta. Discontinuity in the plaque was created by radiating face of ultrasonic probe tip. Paraffin section: hematoxylin-eosin and Gomori trichrome. (Original magnification ×50, reduced by 32%.)

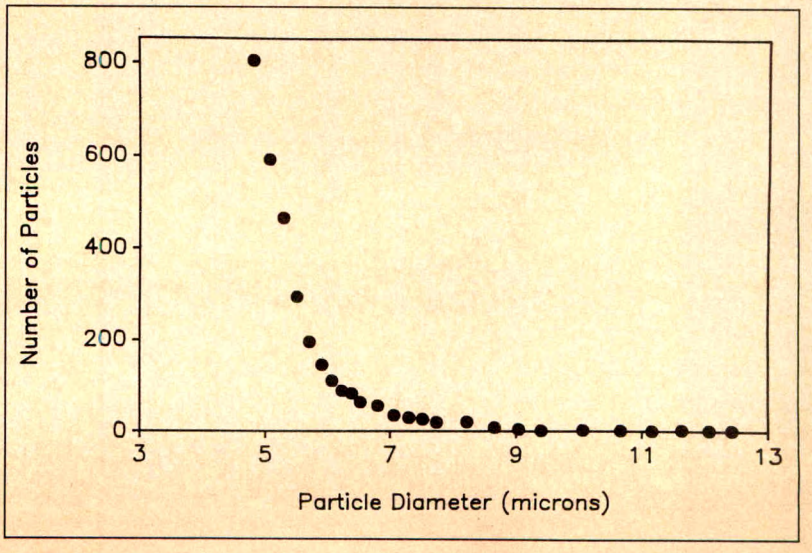


FIGURE 5. A typical distribution curve of particle sizes measured by Coulter technique.

and cholesterol crystals, amorphous fibers and fatty droplets, ranging in diameter from 5.5 to 13.2 μm.

Debris particle sizes: In all, 57,863 particles were counted and measured, and the particle diameters ranged from 4.8 to 15.8 μm. A total of 15 different specimens were counted by Coulter technique. The 15 specimens included 5 aortas after perforation of a normal aortic wall site, 5 aortas after perforation of a fibrous plaque and 5 aortas after perforation of a calcified plaque. The mean debris size did not show significant differences among the 3 categories of exposed targets. Figure 5 shows a representative particle's absolute size distribution. It also shows that the majority of these particles, generated by calcified plaque disruption, were consistently <7 μm in diameter, and >95% of the particles were <11.3 μm.

DISCUSSION

High-intensity ultrasound for atherosclerotic plaque ablation: At the initiation of this study we hypothesized that high-intensity ultrasound had a potential to disrupt the calcified and fibrous human atherosclerotic lesions. We also hypothesized that owing to different acoustomechanical properties, rigid, nonpliable and brittle tissue will disrupt sooner than elastic, distensible and pliable tissue. Results at output setting P_1 supported this hypothesis. Thus, it appears that unlike other currently available techniques, high-intensity ultrasound may be able to disrupt human atherosclerotic plaques "selectively" and, due to the small size of the resulting debris,[12] with potentially less danger of peripheral embolization. Of course, clinically, only effective plaque removal, not perforation of the underlying arterial wall, is desirable. Since the perforation time as measured in this protocol also included the time necessary to perforate the media and adventitia underlying the plaque, the true plaque-only ablation time would be shorter.

This study provides evidence that only at lower energy intensities does ultrasound selectively discriminate plaques from healthy arterial wall. At higher intensities tissues disrupt so quickly that their acoustomechanical differences remain unnoticed. The mechanism of high-intensity ultrasound tissue ablation is poorly understood, but is most likely related to acoustic cavitation.[13–16] Other potential mechanisms, most probably active in concert with cavitation, include direct jackhammer effect, shock-wave induced stress, acoustic microstreaming shearing stress and resonance-related stress.[17]

Study limitations: An important limitation of this study is that it deals with dead tissue and does not provide information about intravital changes within the arterial wall during and after treatment. Also, a tangential rather than perpendicular ultrasound irradiation of the arterial wall would be used in eventual human "ultrasound angioplasty." Furthermore, if the mechanism of atherosclerotic ablation is acoustic cavitation, the physical differences between cavitation in blood and in water suggest the possibility of differences when the fluid surrounding the probe and atherosclerotic plaque is blood rather than water.

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Effect of a Community Cholesterol Screening Program on Serum Total Cholesterol Level

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The National Cholesterol Education Program advocates the importance of "knowing your cholesterol."[1] However, the value of cholesterol awareness has not been tested. This report compares serum total cholesterol levels at baseline and 6 months later of apparently healthy volunteers participating in a cholesterol screening program with levels in control subjects who did not participate in the program.

In November 1987, the Upson County Hospital in Thomaston, Georgia (population 10,000) sponsored a Community Health Fair. As part of the health fair, a voluntary total serum cholesterol test was offered for $3.00. Four hundred nine participating volunteers were advised to have follow-up cholesterol testing free of charge after 6 months. At the same time, 51 control subjects (mostly hospital employees and private patients of one of the authors (TCH)) agreed to have their serum cholesterol tested and to remain unaware of the test result until a 6-month follow-up cholesterol test had been performed. Persons were excluded from the control group if they had knowledge of their serum cholesterol level in the 6 months before baseline test, or if they attended the Community Health Fair.

Pamphlets containing information about hypercholesterolemia were made available to volunteers at the health fair. Study volunteers were told their baseline test results by telephone. Additionally, their test results were forwarded to their personal physicians with a letter describing the baseline test results. Physicians were encouraged in the letter to discuss the test results with the study volunteers. The study coordinators made no specific recommendations to either the volunteers or their physicians regarding the risks of hypercholesteremia or therapeutic options.

Study volunteers and controls were requested to return for a free follow-up test at 6 months. The control group was contacted by telephone and told the baseline and follow-up test results only when the follow-up testing had been completed. Control subjects were eliminated from the study if they had their cholesterol tested between the baseline and follow-up testing.

A follow-up questionnaire was sent to study volunteers who completed follow-up testing asking: (1) Did their doctor discuss their test results with them? (2) Did their doctor make specific recommendations (diet or medications)? (3) Did they begin taking a cholesterol-lowering drug? (4) Did they alter their diet, and (5) if so, for what reason?

All specimens (mostly nonfasting) were analyzed enzymatically on a DuPont Aca(R) discreet clinical analyzer.[2]

Comparison of continuous variables between groups was performed with the independent t *test. Comparison of continuous variables in the same groups (from baseline to follow-up) was performed with dependent* t *test. Discreet variables were compared using chi-square analysis. Differences were considered significant at* $p \leq 0.05$. *Percent changes represent the mean of percent changes in persons. Continuous variables are reported as mean ± standard deviation.*

Eight hundred people attended the Health Fair, of whom 409 volunteered to have cholesterol testing: 303 volunteers (37% men, mean age 60 years) completed the 6-month follow-up test and comprised the study group. Mean cholesterol level was 258 mg% (Table I). Thirty-seven people (58% men, mean age 52 years) were recruited as control subjects completed follow-up testing. Mean serum cholesterol was 224 mg% (Table I). Participants who did not complete follow-up testing had baseline characteristics similar to the participants who did.

From baseline to 6-month follow-up (Table I) statistically significant improvement in cholesterol levels was observed in the older age subgroups of volunteers, and the greatest improvement was observed in volunteers aged >60 years (266 to 235 mg%, −10.2%, $p < 0.001$) *(Figure 1). There was no significant change in serum cholesterol from baseline to follow-up testing in any age subgroup of control subjects.*

From baseline to follow-up there was a shift in individual volunteers from the group with abnormally high cholesterol to the groups with normal and moderately elevated cholesterol (Figure 2). This improvement was not observed in control subjects.

One hundred eighty-eight volunteers (62%) responded to the questionnaire. Volunteers who dis-

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cussed their test results with their doctor had a significantly greater percent improvement at follow-up than those who did not (−11.1 vs −8.4%, p = 0.05). Participants who altered their diet had a greater relative decrease in serum cholesterol at follow-up than those who did not (−10.7 vs −1.6%, p <0.001). The patients who changed their diet in response to their doctor's specific recommendations achieved a significant reduction (−12.7%, p <0.002) at follow-up. Volunteers who altered their diet specifically to lower their cholesterol had significantly greater improvement in cholesterol levels (272 to 241 mg%, −10.5%, p <0.001) than did volunteers who altered their diet for other reasons.

Thus, cholesterol screening at the community level results in significant reduction of short-term follow-up cholesterol levels. The reduction was greatest in older (age >60 years) volunteers with high serum cholesterol

TABLE I Mean Serum Total Cholesterol at Baseline and Six-Month Follow-Up with Percent Change

	Volunteers (n = 303)	Control Subjects (n = 37)	p Value*
Age <40 years			
Number	26	8	
Baseline†	232	212	NS
Follow-up†	228	243	NS
Mean % change per individual	−0.6%	+19.9%	0.03
p Value‡	NS	NS	
Age 40–60 years			
Number	107	18	
Baseline	251	219	NS
Follow-up	233	228	NS
Mean % change per individual	−5.3%	+6.4%	0.002
p Value	<0.001	NS	
Age >60 years			
Number	170	11	
Baseline	266	240	NS
Follow-up	235	256	NS
Mean % change per individual	−10.2%	+7.7%	<0.001
p Value	<0.001	NS	

*Intergroup comparisons.
†Cholesterol values expressed in mg%.
‡Intragroup comparisons.
NS = not significant.

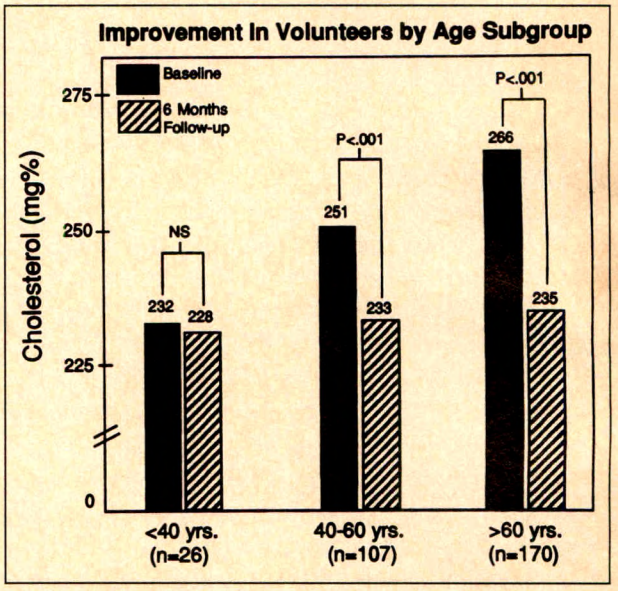


FIGURE 1. Significant reductions in serum cholesterol from baseline to follow-up were observed in the older age subgroups of volunteers. NS = not significant.

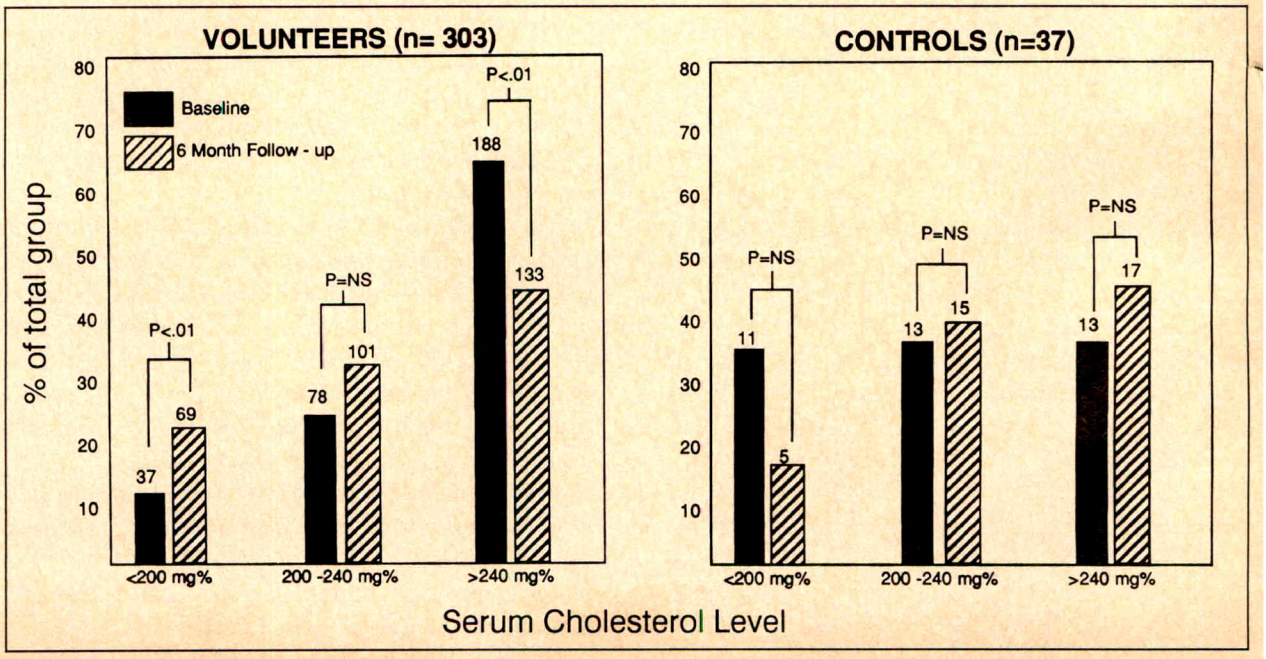


FIGURE 2. Compared with control subjects, the volunteer population demonstrated a significant shift toward the normal cholesterol group from baseline to follow-up. NS = not significant.

(>240 mg%), who discussed their test results with their doctor and who altered their diet or started drug therapy for the specific purpose of decreasing cholesterol. Other studies have reported the results of community-based cholesterol awareness programs[3-5] but have not compared the results of volunteers to control subjects unaware of results. The present study sought to assess a "cholesterol awareness effect" in a controlled manner, and to provide data about the individual response to the cholesterol testing. The significant improvement in the study group compared with control subjects is partially the result of regression to the mean and differences between the 2 groups. However, the very significant improvement in cholesterol levels, especially in patients in the older subgroups who discussed the test results with their physician, validates our conclusion that cholesterol screening resulted in cholesterol reduction.

Wynder et al[3] tested cholesterol levels of 12,432 volunteers in New York City. Forty percent of volunteers in that study responded to the testing with a change in diet compared with 77% in the present study. This may be due to the higher prevalence of hypercholesterolemia in the present volunteer group. Also, in the present study, 41% of volunteers discussed their test results with their physician, and this was associated with reduction of serum cholesterol levels.

The Stanford Three Community Study[4] evaluated the effect of cholesterol awareness and diet modification by performing a health education campaign in 2 communities and comparing the effects on diet and serum cholesterol levels to a control community with no health education campaign. There was a significant decrease in dietary fat consumption in the study cohort compared with the control group at 1 and 2 years. However, the predicted decline in serum cholesterol levels was not observed. The greater improvement in volunteer cholesterol levels in the present study compared to the Stanford study may be attributable to (1) the shorter duration of our study (6 months vs 2 years), (2) the involvement of the local physician, or (3) increased acceptance and availability of low-cholesterol foods in the 1980's compared with the 1970's when the Stanford Study was completed.

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Effect of a Two-Year Public Education Campaign on Reducing Response Time of Patients with Symptoms of Acute Myocardial Infarction

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Earlier application of thrombolytic therapy for acute myocardial infarction (AMI) improves efficacy.[1-5] For maximal benefit, patients must recognize cardiac symptoms and seek care promptly. To determine whether a public education program would improve the public's ability to recognize symptoms of AMI and seek prompt medical attention, thereby reducing delay between onset of symptoms and hospital presentation, we evaluated emergency department records before and after a public education campaign.

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Jacksonville is a town in rural central Illinois with 1 hospital serving a population of 26,000 in town and a total population of 55,000. Baseline data were gathered for 1 year: 9 months from retrospective review of emergency department charts, and 3 months prospectively. We selected 80 complaints commonly suggestive of AMI (Table I). The study population consisted only of persons reporting to the emergency department with 1 or more of these 80 complaints. Records of persons who did not report any of the 80 target symptoms are not included in this study. A 1-year public education program, targeted at the entire population, was instituted at a cost of $10,000, which was felt to be a reasonable cost expenditure for a medium-size hospital. The program consisted of patient edu-

TABLE I Complaints Evaluated

Angina	Chest pain, numbness	Lifeline
Arm pain with nausea	Chest pain, shoulder pain	Left rib pain (nontrauma)
Arm + neck pain with dizziness	Chest pain, vomiting	Loss of consciousness
Back pain radiating to sternum	Chest pressure	Man down
Blacked out	Chest problems	Neck pain
Cardiac, shoveling snow	Chest spasm	Base of neck + shoulder pain
Cardiac arrest	Chest tightness	No BP, diaphoretic
Collapsed	Pain chest, hands, arms, back	Pain around heart
Chest discomfort/hurts	Chest wall pain	Pain in throat with radiation
Chest heaviness	Code 70 (arrest)	Pain across shoulder blades
Chest hurts + tight	Epigastric pain	Pain in stomach + left back
Chest pain	Fullness feeling in chest, ? heart	Pain in shoulders with difficulty breathing
Chest pain with abdominal pain	Heart attack	Passed out/passing out
Chest pain, burning	Heart burn	Possible cardiac
Chest pain, choking	Heart condition	Problem with chest
Chest pain-emphysema	Heart doesn't feel right	Left shoulder pain
Chest pain especially after eating	Heart pain	Shortness of breath + pain in left arm
Chest pain, left shoulder pain	Heart problem	Sick heart
Chest pain, weak	Hurting in chest	Stomach pain with dizziness
Chest pain + back pain	Indigestion	Stomach pain with or without vomiting
Chest pain + back pain + shortness of breath	Jaw pain	Tightness in chest
Chest pain, sick all over	Left elbow pain	Throbbing in chest
Chest pain, shoulder + back pain	Left arm burning	Upper abdominal pain
Chest pain, rapid pulse	LUQ pain	Unresponsive
Chest pain, fell to floor	Left arm pain	Unconscious
Chest pain, faint	Left back pain	Not responding
Chest pain, dizzy, headache	Left breast pain with shortness of breath	Unstable angina
Chest pain, difficulty breathing		

BP = blood pressure; LUQ = left upper quadrant.

TABLE II Two-Year Public Education Campaign

800	Brochures distributed
15,500	Brochures mailed
50	Posters displayed at local businesses + in hospital lobby
23	Television spots (2 television stations)
358	Radio spots (4 radio stations)
426	Public service announcements (3 radio stations)
42	Newspaper spots (5 newspapers)
4	Radio talk shows
2	Public speaking engagements
1	Article in senior citizen publication

The telephone directory had a chest pain information page. Brochures were provided in magazine racks throughout the hospital.

TABLE III Minutes from Onset of Symptoms to Emergency Room Arrival

Discharge Diagnosis	Before Education	First Year After Education	Second Year After Education
Angina	n = 114 204 ± 320 m = 103	n = 168 176 ± 219 m = 103	n = 144 234 ± 441 m = 117
Myocardial infarction	n = 66 217 ± 267 m = 103	n = 67 252 ± 315 m = 100	n = 66 175 ± 217 m = 112
Noncardiac chest pain	n = 320 248 ± 302 m = 125	n = 433 248 ± 347 m = 108	n = 415 239 ± 316 m = 120

cation brochures, television advertisements, newspaper advertisements, public talks, posters, and radio spots (Table II). Radio public service announcements were aired at low-priority listening times, whereas paid media spots were concentrated at high-priority times. After an initial heavy thrust during the first 2 months, the messages were staggered throughout the remainder of the campaign. The program explained the warning signs of a heart attack and the need to seek prompt medical attention if they occurred.

The public education continued for a second year using the same media avenues donated at no cost. Emergency department patient charts were reviewed weekly during the 2 years of education. Emergency department records of all patients admitted with 1 of the 80 cardiac symptoms were reviewed. The results were analyzed to detect: (1) inappropriate increases in patient visits for chest pain (i.e., has public education unduly increased public anxiety regarding chest pain so as to overwhelm the emergency department with noncardiac chest pain admissions?); (2) early arrival of patients with definite AMI; and (3) early arrival of patients with angina or other cardiovascular illnesses.

The study population before and after education is comparable, with a mean age of 57 and 55 years, respectively, and the percentage of men and women remained constant at 45 and 55%, respectively, all 3 years. The education campaign did not improve patient response time of patients with chest pain (Table III). We categorized numerous subgroups of patients with angina or AMI by age, sex, or presentation to the emergency department in < or >6 hours after onset of

pain and analyzed the results. We found no significant earlier presentation.

The small increase in number of emergency department visits during the 3-year study was not statistically significant and was probably related to the closure of 2 small rural hospitals 23 and 25 miles away from Jacksonville during the time of the 2-year education program. The percentage of the study population that resulted in noncardiac complaints increased 26% from baseline during the study period.

It would be somewhat nihilistic to assume that a public education program is of no value. However, public behavior on a broad basis is difficult to change. Our impression after this study is that earlier response time with chest pain may require a more prolonged public education effort. Our results are similar to the study of Ho et al[6] in Seattle, Washington, in which a short-duration education campaign was used. Public education efforts in Goteborg, Sweden, and in Canada did obtain positive results, which may be attributed to different public education methods and social differences.[7,8]

In conclusion, a major public education campaign in a self-contained rural community over a period of 2 years did not result in either a major inappropriate increase in patients presenting with anxiety regarding chest pain or a major decrease in the amount of time that the average patient came in with evidence of AMI or other cardiac complaints after initially experiencing these symptoms.

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Reducing Delay in the Emergency Room in Administration of Thrombolytic Therapy for Myocardial Infarction Associated with ST Elevation

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Thrombolytic therapy reduces mortality and improves left ventricular function in patients with acute myocardial infarction (AMI).[1–5] Our review of 816 patients treated in community hospitals showed that the primary care or emergency physician can use these drugs effectively, but we also found that the average delay from arrival in the emergency department to institution of thrombolytic therapy was 86 minutes.[6] This is similar to other cities, in which an average time from arrival in the emergency department to time of treatment was 84 minutes.[7] We began this study to see if the time delay between patient presentation to emergency department and institution of thrombolytic therapy could be reduced.

From July 1, 1988, to June 30, 1989, patients admitted to the emergency department at St. John's Hospital, Springfield, Illinois, with AMI were monitored, and duration of time from admission to administration of thrombolytic therapy was recorded. St. John's Hospital is a 731-bed teaching hospital with an emergency department staffed by emergency physicians. Beginning July 1, 1989, special efforts were made to increase the speed of therapy. These included the following steps. (1) Standard thrombolytic therapy protocols were kept in the emergency department for rapid use and reference. (2) The medical staff approved the concept that the emergency physician

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TABLE I Results

	No. of Pts	Admission to Therapy (min)	p Value
Initial baseline period	28	70 ± 26	NS
First efficiency attempt	17	66 ± 30	NS
Second efficiency attempt	6	34 ± 5	<0.05

NS = not significant.

should institute thrombolytic therapy for all patients presenting with AMI (without contraindications) as rapidly as feasible, and was not to delay therapy to notify the primary care physician or cardiologist, unless equivocal clinical findings indicated the need for the consultation. (3) Therapy was to be started in the emergency department and not after transfer to the Intensive Care Unit (therapy was generally administered in the emergency department during the baseline period anyway). (4) The commonly used thrombolytic agents were stored in the emergency department so that rapid mixing and administration could be performed. (5) Consent was simplified to either rapid verbal consent or a simple 3-paragraph consent form. (6) The chest x-ray was performed after the decision regarding thrombolytic therapy had been made, unless dissecting aortic aneurysm was considered to be in the differential diagnosis. (7) A computerized lab panel request was arranged so that multiple routine lab work could be obtained with a single order. (8) The emergency physicians were instructed not to wait for laboratory studies, including cardiac enzymes or bleeding studies, before making a decision regarding thrombolytic therapy. Therapy was based on the electrocardiogram and clinical history. (9) The goal was established to have the electrocardiogram completed within 5 minutes of arrival to the emergency department for patients with chest pain. Emergency department technicians and nurses were trained to do this, and an electrocardiogram machine was maintained in the emergency department for immediate use. (10) Posters illustrating electrocardiographic patterns of anterior and inferior AMI were placed in the holding rooms for chest pain patients for comparison of the patient's electrocardiogram. These posters also included indications and contraindications for thrombolytic therapy. (11) A second nurse was routinely freed to assist the physician with the rapid diagnosis of patients with chest pain and administration of thrombolytic therapy if required. These changes were implemented beginning July 1, 1989, and were fully in force by the end of the year. Despite this, little change was noted during the entire year from July 1, 1989, to June 30, 1990. By July 1, 1990, hospital administration had become actively involved in coordinating the efforts of the emergency physician, nursing staff, medical staff and technical support staff, including electrocardiogram technicians and pharmacy. This led to a twelfth recommendation. (12) An efficiency committee was formed to implement the preceding protocol for managing patients with chest pain and suspected AMI, to conduct inservice training for emergency department staff and to review results on a bimonthly basis.

The rapid application protocol was activated for any patient admitted to the emergency department with chest pain. Those with electrocardiographic evidence or criteria for AMI were given thrombolytic therapy if clinically appropriate with no contraindications. Patients with equivocal electrocardiographic findings or non-Q-wave AMI were not included in this protocol. Statistically significant differences among the different groups were determined using 1-way analysis of variance and Duncan's multiple range testing. A p value <0.05 was considered statistically significant.

During the baseline period (from July 1, 1988, to June 30, 1989), 28 consecutive patients with AMI were treated with thrombolytic therapy. The time from admission to administration of therapy was 70 ± 26 minutes (Table I). The next 17 patients, admitted during the first efficiency attempt, from July 1, 1989, to June 30, 1990, were treated during the initial phases of administrative changes in the emergency department; the interval between admission and therapy did not result in any significant improvement, but remained at a mean of 66 ± 30 minutes (Table I).

The second efficiency attempt, from July 1, 1990 to December 31, 1990, which included aggressive administrative support and the efficiency committee review, led to a significant reduction in time from admission to administration of therapy, 34 ± 5 minutes (Table I). This was significant, with p <0.05. Beginning in 1990, 12 patients were enrolled in a competing study designed to evaluate the role of direct angioplasty in the setting of AMI; these patients were not included in analysis. Treatment of these 12 patients by direct angioplasty explains the decrease in number of patients treated with thrombolytic therapy during this study period.

Earlier administration of any thrombolytic agent improves efficacy.[1–5] Proposed approaches to expedite administration of thrombolytic therapy include paramedic initiation of lytic therapy in the field, electrocardiogram transmission from the field, and more efficient management in the emergency department.[8,9] Others have identified delays in the emergency department that can be

changed to hasten delivery of therapy.[10] In the current study a common-sense protocol that reduced time from patient admission to administration of thrombolytic therapy became effective with the establishment of an emergency department efficiency committee. Delay in treatment of AMI is a problem nationwide.[6–9] Improved efficiency will mean a basic change in practice pattern. A major hurdle for most will be a commitment to treatment of patients with thrombolytic therapy in the emergency department, and by emergency physicians,[10] and effecting change in established practice routine.

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Results of Percutaneous Transluminal Angioplasty of the Left Main Coronary Artery

Michael Eldar, MD, Nancy Schulhoff, RN, Izhak Herz, MD, Robert Frankel, MD, Harry Feld, MD, and Jacob Shani, MD

Percutaneous transluminal coronary angioplasty (PTCA) of the left main coronary artery (LMCA) carries relatively high rates of immediate and long-term morbidity and mortality.[1] Patients with LMCA stenosis can be divided into 2 groups: protected (defined as the existence of at least 1 patent bypass graft to the left anterior descending or circumflex artery), and unprotected. A recent report by an American College of Cardiology/American Heart Association task force regards PTCA of unprotected LMCA absolutely contraindicated.[2] Yet, for critically ill patients whose operative risk is prohibitive, PTCA of unprotected LMCA may be a "last resort" option. We report our immediate and long-term follow-up results.

We identified retrospectively all patients who underwent elective angioplasty of the LMCA from January 1985 to August 1990. The information on the patients was collected from hospital charts, a PTCA database, and cineangiographic films. Follow-up information was obtained from outpatient charts and telephone interviews with patients and family physicians. Of 2,190 PTCA procedures performed during the study period, elective angioplasty of LMCA (i.e., in patients who had unstable angina associated with significant LMCA narrowing that were refused coronary artery bypass grafting due to excessive risk) was performed in 16 patients. All patients were in New York Heart Association class III to IV, had poor left ventricular function (ejection fraction <30%) and had >70% stenosis of the LMCA in at least 2 angiographic projections. Coronary artery bypass surgery had been performed previously in 11 patients, and 8 patients had patent graft(s) to either the left anterior descending and/or circumflex coronary artery. An intraaortic balloon pump was inserted prophylactically in 2 patients and cardiopulmonary support was instituted prophylactically in 1 patient. Successful PTCA was defined as a <40% residual luminal stenosis in 2 or more angiographic projections.

Baseline characteristics were similar (except for mean age) in protected and unprotected patients (Table I). All LMCAs were successfully dilated, with the mean stenosis reduced from 87 ± 8 to 17 ± 13%. None of the patients had acute myocardial infarction, urgent bypass surgery or died during or within 24 hours of PTCA. One patient died 9 days after the procedure due to pneumonia. Follow-up data were obtained on all patients (Table I). During a follow-up period of 6 to 54 months (24 ± 15), only 1 patient died due to pump failure after bypass surgery, 4 months after PTCA. Six patients (3 with protected LMCA) had repeated angiography (2 to 40 months after the PTCA) due to recurrent angina pectoris. Restenosis of LMCA (50% reduction in luminal diameter after PTCA) was found in 4 patients. Revascularization procedures were performed in 6 patients (38%) during the follow-up period, and were equally distributed among the groups.

All surviving patients reported significant clinical improvement, although 12 patients still suffer from class II stable angina pectoris.

The main finding of the current study is that angioplasty of the LMCA is beneficial and relatively safe in selected patients. Our results are similar to those of Stertzer et al,[3] but differ from those of O'Keefe et al.[1] In the latter study, 26 patients who underwent elective angioplasty of unprotected LMCA had 9.1% acute and 65% late mortality rates. The relatively long inflation times used in our laboratory[4] may have contributed to our favorable results.[5,6] Most of our patients underwent PTCA without intraaortic balloon pump or cardiopulmonary support. In fact, analysis of our data in high-risk

TABLE I Characteristics of Study Patients

	Protected	Unprotected
No.	8	8
Sex (M/F)	7/1	4/4
Age*	67 ± 9	78 ± 6
LMCA stenosis (%)	90 ± 9	84 ± 5
Angioplasty to additional coronary arteries (no.)	6	3
Intraaortic balloon pump	1	1
Cardiopulmonary support	—	1
Angioplasty of LMCA		
No. of inflations	5 ± 2	5 ± 2
Duration of longest inflation	137 ± 89	86 ± 40
Residual LMCA stenosis (%)	19 ± 16	15 ± 11
Follow-up		
Early death (≤ 1 month)	0	1
Late death	0	1
Coronary bypass surgery	1	1
Coronary angioplasty	2	2
Angina pectoris	7/8	5/8

*$p \leq 0.01$.
Results are given as mean ± standard deviation.
LMCA = left main coronary artery.

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patients suggests that support devices may be associated with an increased morbidity and mortality.[7]

This study demonstrates that angioplasty of LMCA stenosis can be performed with a high success rate and suggests that angioplasty of unprotected LMCA is a viable option for patients with prohibitive surgical risk. However, the data should be interpreted cautiously, since selection bias and a relatively small number of patients may have contributed to these favorable results. Furthermore, close follow-up is essential because a high restenosis rate may occur in these patients,[1] and a significant proportion of these patients require additional revascularization procedures during the ensuing years.

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Symmetry, Broken Symmetry, and Restored Symmetry of Apparent Pure Ventricular Parasystole

Agustin Castellanos, MD, Pedro Fernandez, MD, Federico Moleiro, MD, Alberto Interian, Jr., MD, and Robert J. Myerburg, MD

Previous reports dealing with the dynamics of "pure" parasystole using mathematic and electronic (pacing-induced) models, respectively, showed that a number of predictions emerged naturally from mathematic analysis.[1,2] Therefore, it appeared of interest to determine whether they would also apply to a series of patients with clinical (apparently) "pure" ventricular parasystole who were monitored for relatively long periods of time. In contrast to previous studies, Glass et al[1] had the ingenious idea of analyzing the number of sinus beats interposed between 2 consecutive manifest parasytolic beats. They observed that, with the rates being practically constant, a detailed mathematic description could be made using 2 parameters: the ratio of ectopic cycle length to sinus cycle length and the ratio of ventricular refractory period to sinus cycle length. From a correlation of these parameters 3 basic rules emerged: (1) There are at most 3 different values for the number of sinus beats in between parasystolic beats. (2) Only 1 of these values is odd. (3) The sum of the 2 lesser values is 1 less than the larger value.

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We attempted to determine whether symmetry (a term extrapolated from Kaku and Trainer,[3] here meaning that sinus and parasystolic rhythms could be linked by the aforementioned mathematic rules) was present in 10 cases in whom continuous ventricular parasystole had been reprospectively identified. In 9 patients, the diagnosis was made by 24-hour Holter recordings and in 1 the diagnosis was made by long (1 to 3 minutes) rhythm strips obtained at frequent intervals from a coronary care unit monitoring device.

Table I lists the pertinent information. In the manner of Glass et al,[1,2,4] we defined the refractory period as the shortest interval between a sinus-induced QRS complex and a parasystolic beat. We attempted to identify symmetry once the diagnosis of parasystole had been made, when sinus cycle length and ectopic cycle length were first found to be "constant" (i.e., with variations of <±5%). We found symmetry in all patients.[3] At the time at which this initial symmetry occurred, the refractory period ranged between 380 and 540 ms and the ectopic cycle length between 1,040 and 2,330 ms. The ectopic cycle length/sinus cycle length ratio varied between 1.58 and 2.74 and the refractory period/sinus cycle length ratios between 0.43 and 0.64. When these values were plotted in the refractory period/sinus cycle length, ectopic cycle length/sinus cycle length plane used by Glass et al,[1]

TABLE I Values, Ratios and Symmetries of Apparent Pure Parasystole

Pt.	TE/TS Ratio	RP/TS Ratio	Symmetry: Numbers	TE	TS	RP
1	1.63	0.59	1, 2, 4	1,040	640	380
2	1.68	0.50	1, 2, 4	1,280	760	380
3	1.65	0.50	1, 2, 4	1,320	800	400
4	1.73	0.60	1, 2, 4	1,210	700	420
5	1.58	0.43	1, 2, 4	1,520	960	410
6	1.59	0.47	1, 2, 4	1,480	930	440
7	2.74	0.64	2, 7, 10	2,330	850	540
8	2.39	0.56	2, 7, 10	2,220	930	520
9	2.24	0.54	1, 6, 8	1,500	670	360
10	2.23	0.49	1, 6, 8	1,920	860	420

RP = refractory period; TE = ectopic cycle length; TS = sinus cycle length.

they yielded the expected number of sinus beats between consecutive manifest parasystolic beats (hereby considered as the numbers of symmetry). These values were the same as those directly counted on electrocardiographic paper running at a speed of 25 mm/s (Table I). Although the latter was that at which all measurements were performed, some illustrations will be presented at slower paper speeds since they were those at which 1 or more minutes of recording time could be best presented as a single figure. The numbers of initial symmetry were 1, 2 and 4 in 6 patients; 2, 7 and 10 in 2 patients; and 1, 6 and 8 in 2 patients. However, in all patients this initial symmetry was broken and subsequently restored.[3,6]

An example is shown in Figure 1. It shows the well-known characteristics that for many years have been attributed to "pure" parasystole.[5] *In this example, where the corresponding ratios were 0.59 and 1.63, respectively, the X in the corresponding region indicated the predicted 3 values (1, 2 and 4), which were precisely the number (in parentheses, below the rhythm strip) of hand-counted sinus beats between manifest parasystolic beats. In Figure 2, ectopic cycle length was 2,330 ms; sinus cycle length, 850 ms; and refractory period, 540 ms. Thus, the corresponding ectopic cycle length/sinus cycle length and refractory period/sinus cycle length ratios had values of 2.74 and 0.54, respectively. Consequently, the numbers of initial symmetry were 2, 7 and 10.*[1] *Figure 3 (top), obtained 40 seconds later, at a slower paper speed (with each horizontal line representing 20 seconds of recording time), reveals that when sinus cycle length varied erratically (increasing and decreasing), the symmetry was broken, since number 13 appeared several times (instead of number 10).*[3,6] *However, when the initial conditions (previous values) recurred 2 minutes later, the preexisting symmetry was restored, as can be seen in the lower panel where the number of sinus beats between parasystolic beats was again 2, 7 and 10.*[3]

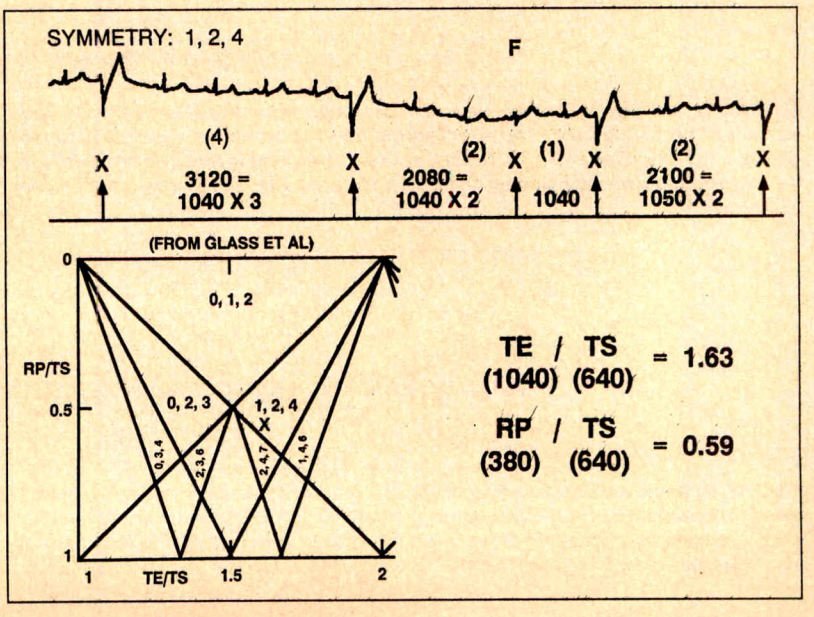


FIGURE 1. Apparent "pure" ventricular parasystole. Tracing obtained at a paper speed of 25 mm/s. The diagram, from Glass et al,[1] depicts the mathematically predicted number of sinus beats in between ectopic beats in the refractory period (RP)/sinus cycle length (TS), ectopic cycle length (TE)/TS plane for pure parasystole. For each region, the allowed values are indicated by 3 integers. The location X in parameter space corresponds to the predicted numbers in this case (1, 2 and 4) that coincide with the numbers of directly counted interposed sinus beats. The latter (numbers of symmetry) are shown in *parentheses* below the rhythm strip, where the corresponding time intervals are expressed in milliseconds. F = fusion beat (also considered a manifest discharge)[1]; X = morphology of totally manifest parasystolic discharges. (Reproduced with permission from the American Physiological Society.)

Figure 4 (top) depicts how the initial symmetry was lost for other reasons.[2] It occurred when sinus cycle length changed, but not erratically.[2] Note that sinus cycle length decreased persistently (to 900 ms) whereas ectopic cycle length and refractory period remained constant. Therefore, the ectopic cycle length/sinus cycle length ratio and the refractory period/sinus cycle length ratio became 2.59 and 0.53, respectively.[1] Consequently, in the refractory period/sinus cycle length, ectopic cycle length/sinus cycle length plane of Glass et al, there was a shift to the 2, 4, and 7 zone. The initial symmetry recurred when the cycle length again increased to the original values so that the initial conditions resumed (bottom).

Our report corroborates that predictions regarding the number of sinus beats between parasystolic beats could be made for a group of patients with apparent "pure" ventricular parasystole. This had been reported by Gordon et al[2] in a patient having parasystole with "weak" modulation. Moreover, in a study of modulated parasystole, Courtemanche et al[4] noted that rhythms associated with quasiperiodicity obeyed the rules derived

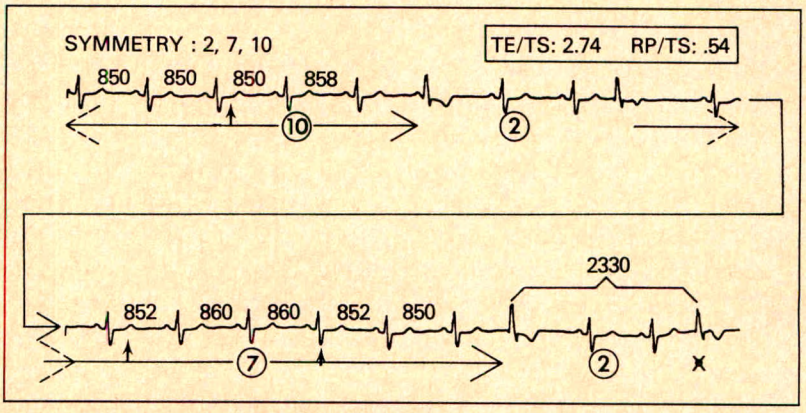


FIGURE 2. Apparent "pure" ventricular parasystole. Recordings were obtained at a paper speed of 25 mm/s. The 2 strips are continuous. The numbers circled (2, 7 and 10) represent the numbers of symmetry, i.e., of sinus beats interposed between consecutive manifest parasystolic beats. The *arrowhead* at the beginning of the *top* indicates that there were 5 additional sinus beats between the immediately preceding manifest parasystolic discharge (not shown) and the first discharge (X) seen in this figure. Abbreviations as in Figure 1.

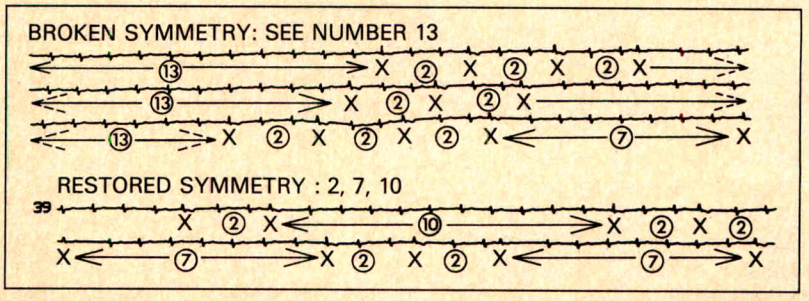


FIGURE 3. Same patient as in Figure 2; recordings were obtained at a slower paper speed. Each *horizontal line* represents 20 seconds of recording time. *Top panel* shows that the symmetry was lost because number 13 (instead of 10) appeared 3 times during 1 minute. This occurred when the sinus cycle length changed erratically. In the *bottom 2 strips*, the preexisting symmetry was restored when the initial conditions resumed (the sinus cycle length again attained a constant value similar to the preexisting value).

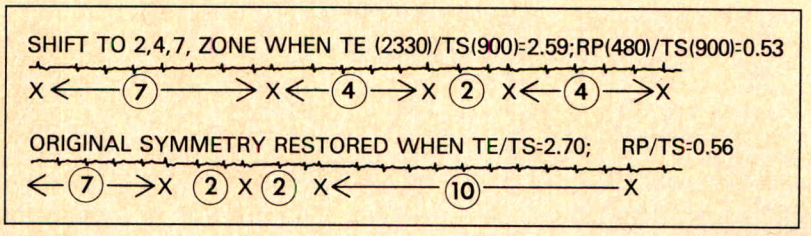


FIGURE 4. Same patient as in Figures 2 and 3. Loss of the preexisting symmetry occurring when the sinus cycle length (TS) increased consistently *(top)*. This caused in the RP/TS, TE/TS plane, of Glass et al,[1] a shift to the 2, 4 and 7 zone. Note that these were precisely the number of sinus beats interposed between manifest parasystolic beats. *Bottom*, the preexisting symmetry was restored when the initial conditions resumed (TS became persistently shorter). Abbreviations as in Figure 1.

for "pure" parasystole. They also observed that these rules were also fulfilled in some sporadic cases reported by other investigators.

The mathematic relation under consideration — symmetry — was found in all our patients.[3] Precisely, its identification, not the exact moment at which parasystole was diagnosed, was considered as the starting point of the current study. However, initial symmetry did not last for long periods of time (only minutes), considering that the tracings were obtained for 24 hours. A review of the tapes showed that the lost symmetry resulted from the fact that the physiologic parameters tended to change as time went by. Of the 3 pertinent parameters, we have observed that in absence of exit block, refractory periods tended to be constant. Yet, sinus cycle length and ectopic cycle length (the former more than the latter) were seen to be changing variables. In fact, it is well known that sinus cycle lengths show frequent fluctuations. Moreover, parasystolic cycle lengths are also not constant, but less so than the former.[5] Although not analyzed as such in this study, it is possible to consider that during a 24-hour period parasystole shows not 1 but several symmetries, with the corresponding numbers depending on the different values that the changing parameters attain throughout the monitoring time (Figures 2 and 4).

Finally, in our patients, the possibility that the arrhythmia diagnosed as "pure" parasystole may have been parasystole with "weak" modulation cannot be completely excluded. Because there were some variations in parasystolic cycle lengths during the overall (long-term) recording time, fluctuations attributed to changes in the timing of automatic discharges could have reflected lesser degrees of modulation than degrees of variations of automaticity. However, this in no way would invalidate our study since, as previously mentioned, "weak" modulation may obey the rules of pure parasystole.[2,4]

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Effects of Amiodarone on Serum Lipoprotein Levels

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Amiodarone is an antiarrhythmic agent approved for the treatment of recalcitrant ventricular arrhythmias. It is an amphiphilic-iodinated organic compound with a prolonged elimination rate, and has been associated with a high incidence of thyroid dysfunction.[1] In a previous evaluation of the effects of amiodarone, serum cholesterol was monitored as a systemic marker for thyroid dysfunction.[2] Unexpectedly, there were uniform increases in serum cholesterol independent of thyroid hormone status. Controversy exists as to whether there are changes in serum cholesterol levels in patients receiving amiodarone,[2–6] and it is important to define the action of this drug on high-risk patients who already have heart disease.

Twenty-seven patients (15 men and 12 women: 18 with paroxysmal ventricular tachycardia, 6 with multiform ventricular arrhythmias associated with arteriosclerotic cardiovascular disease and 3 with symptomatic atrial fibrillation; mean age ± standard error of the mean 70 ± 2 years) who required amiodarone for the control of severe symptomatic arrhythmias were followed prospectively. The clinical procedures for monitoring for efficacy and adverse reactions were described previously.[2] Amiodarone was given at a loading dose of 400 to 600 mg/day initially followed by a maintenance dose of 200 mg/day. If the arrhythmia was refractory as assessed by electrocardiography and ambulatory monitoring or by exercise testing, the initial dose was repeated. When necessary the maintenance dose was titrated upward. The maintenance dose was also adjusted downward according to adverse side effects, predominantly symptomatic bradycardias. Many patients with arteriosclerotic cardiovascular disease had underlying hypercholesterolemia, and 3 had been receiving stable doses of gemfibrozil; 3 had started receiving lovastatin either previously (n = 1) or at baseline (n = 2) concomitantly with the amiodarone. Fifteen subjects were receiving thiazides and 2 were receiving estrogens; these medications were started before the amiodarone and

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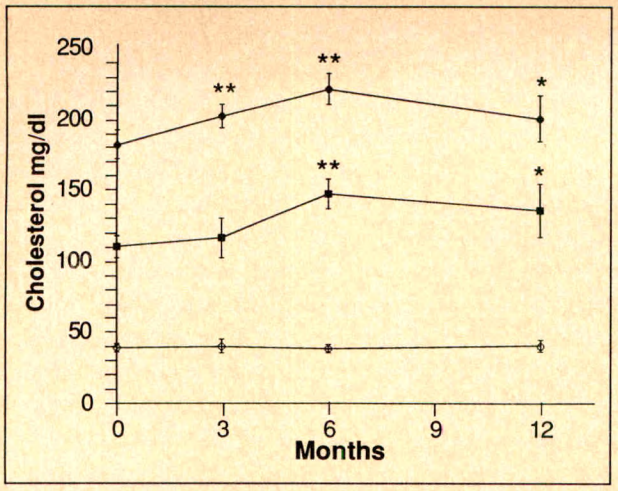


FIGURE 1. The effect of amiodarone on lipoprotein levels. Total *(closed circles)*, low-density lipoprotein *(closed squares)*, and high-density lipoprotein *(open circles)* cholesterol were determined at baseline (n = 20), 3 months (n = 10), 6 months (n = 15) and 12 months (n = 11) in patients receiving amiodarone. Values shown are mean ± standard error of the mean. *p <0.05; **p <0.01.

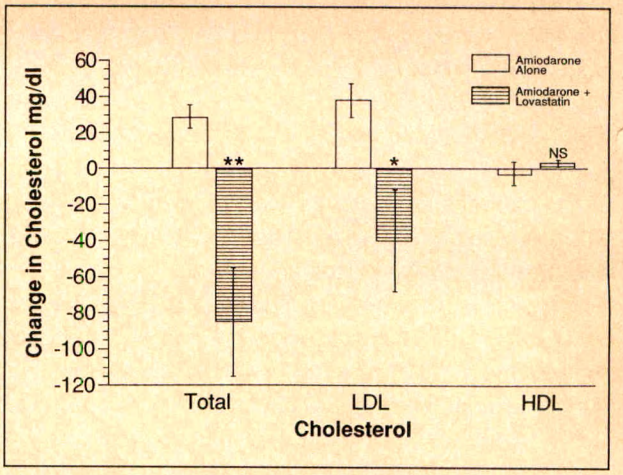


FIGURE 2. Change in lipoprotein levels after 6 months of therapy with amiodarone. The change in total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol at 6 months compared with baseline levels are shown for 15 subjects receiving amiodarone *(open bars)*; the change in these values for 3 subjects taking amiodarone and lovastatin are shown by the *horizontal bars*. Values shown are mean ± standard error of the mean. *p <0.05; **p <0.01. NS = not significant.

continued during the follow-up period. Three subjects became hypothyroid and 1 became hyperthyroid during the course of the follow-up and were treated with L-thyroxine or methimazole, respectively. Blood tests for total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were obtained in the fasting state using standard clinical assays. Data were analyzed as paired and non-paired parametric tests using the Student t *test on a DEC Vax 11/750 computer using the statistical package of RS/1 (BBN Software, Cambridge, Massachusetts).*

Twenty-seven subjects were followed prospectively for a mean of 13 months (range 3 to 24). The mean maintenance dose of amiodarone ± standard error of the mean was 200 ± 23 mg/day (range 200 mg every other day to 400 mg/day). The patients who developed thyroid abnormalities are not included in the further analyses. The 3 patients who were receiving lovastatin are considered separately. Of the 20 remaining subjects, there were statistically significant changes from baseline in total cholesterol at 3 and 6 months and significant changes from baseline in LDL cholesterol at 6 months. These changes in total and LDL cholesterol appeared to be sustained for the 12 months, although the elevated levels achieved borderline significance at 12 months ($p = 0.02$ and $p = 0.05$, respectively) due to the limited number of patients evaluated at this time ($n = 11$) (Figure 1). At 6 months the total cholesterol increased from a baseline of 182 ± 10 to 221 ± 11 mg/dl ($p = 0.001$) and LDL cholesterol increased from 110 ± 8 to 147 ± 10 mg/dl ($p = 0.03$). There was no change from baseline levels in the serum HDL to the levels at 6 months, 41 ± 14 and 38 ± 11 mg/dl, or triglyceride levels, 180 ± 31 and 172 ± 29 mg/dl. The serum level of thyroxine increased from 8.7 ± 0.5 to 10.0 μg/dl at 6 months ($p = 0.001$), although there was no change in serum thyroid-stimulating hormone.

In the 3 subjects treated with lovastatin there was a decrease in total and LDL cholesterol at 6 months when compared to the response of the subjects receiving amiodarone alone (Figure 2). There was no difference in the response to HDL cholesterol. There was no difference in the response of the 3 receiving gemfibrozil from the subjects receiving amiodarone alone, but there are too few subjects to eliminate a type 2 error.

These observations confirm the results that we[2] and others have described, suggesting that amiodarone increases serum cholesterol.[3,6] This study also expands on the short-term, 6-week evaluation of Kasim et al,[6] which demonstrates that the major change in total cholesterol is due to an increase in the LDL fraction. Sonnenblick et al[4] did not note any increase in cholesterol at 30 and 90 days in subjects who were excluded if they had an underlying lipid disorder.

The cause of the elevation of the serum cholesterol is unknown. Although the patients continued to be euthyroid, it is possible that the amiodarone causes a state of intracellular hypothyroidism.[2] Amiodarone also accumulates in the liver and may interfere with intracellular lipid metabolism.[1,6] The prolonged elevation of serum cholesterol induced by amiodarone would be a further

burden on these patients with underlying heart disease, and serum cholesterol should be monitored. Three subjects who needed to continue receiving amiodarone were simultaneously treated with lovastatin. There were no untoward effects of the lovastatin-amiodarone combination, but further patients need to be followed before recommendations may be given. Since submission of this manuscript, investigators noted increases in total cholesterol and apoprotein B levels independent of changes in thyroid function in patients receiving amiodarone (Wiersinga WM, Trip MD, van Beeren MH, Plomp TA, Oosting H. An increase in plasma cholesterol independent of thyroid function during long-term amiodarone therapy. A dose-dependent relationship. *Ann Intern Med* 1991;114:128–132).

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Usefulness of Total 12-Lead QRS Voltage for Determining the Presence of Left Ventricular Hypertrophy in Systemic Hypertension

Luis Rodríguez Padial, MD

The total QRS voltage from all 12 electrocardiographic leads has been evaluated as a criterion for left ventricular (LV) hypertrophy in different disease states.[1,2] The upper limit of total QRS voltage has been established in adults free of cardiopulmonary disease by necropsy criteria.[3] Nevertheless, no study on the use of this criterion in essential hypertension has been performed. Such was the purpose of this study.

M-mode and 2-dimensional echocardiograms and 12-lead electrocardiograms (10 mm = 1 mV) were obtained in 74 consecutive patients (in order of when they were diagnosed) with essential hypertension (blood pressure >140/90 mm Hg) seen in a general hospital. Patients with heart diseases (valvular heart disease, cardiomyopathy, coronary artery disease, and so forth) and inconclusive echocardiograms were excluded, as well as subjects with left bundle branch block, other intraventricular conduction defects or preexcitation in the electrocardiogram. LV mass was calculated using the Penn conventions.[4] LV mass (g) = 1.04 [(LVID + PWT + VST)^3 − LVID]^3 − 13.6, where LVID = end-diastolic LV internal dimension; PWT = end-diastolic posterior wall thickness; and VST = end-diastolic ventricular septal thickness. LV mass ≤131 g/m^2 (men) or ≤100 g/m^2 (women) was considered normal.[5] Because we previously used LV mass ≤215 g as normal,[6] we considered this criterion also. The amplitudes of the QRS complexes were measured from the peak of the R wave to the nadir of either the Q or the S wave, whichever was deeper, according to the method of Siegel and Roberts.[1] The correlation (Pearson) and linear regression between total 12-lead voltage and LV mass has been studied. The use of other electrocardiographic criteria of LV hypertrophy has been studied in these patients and has been previously published.[6]

Blood pressure was 157 ± 15 mm Hg (systolic) and 100 ± 5 mm Hg (diastolic). Among the 74 pa-

TABLE I Results of Total 12-Lead QRS Voltage Criterion (several cutoff points)

ECG Criteria — QRS 12 Leads (mm)	Patients with LV Mass >215 g (n = 46)	Patients with LV Mass <215 g (n = 28)	Sensitivity	Specificity	Accuracy
>175	13	3	0.28	0.89	0.51
>170	14	3	0.30	0.89	0.53
>165	15	5	0.33	0.82	0.51
>160	16	5	0.35	0.82	0.53
>155	22	6	0.48	0.79	0.59
>150	22	6	0.52	0.79	0.59
>145	24	8	0.57	0.71	0.59
>140	26	8	0.63	0.71	0.62
>135	29	10	0.67	0.64	0.64
>130	31	12	0.72	0.57	0.64
>125	33	13	0.80	0.54	0.65
>120	37	13	0.80	0.54	0.70
>115	37	17	0.80	0.39	0.65
>110	39	17	0.85	0.39	0.68
>100	44	23	0.96	0.18	0.66

ECG = electrocardiographic; LV = left ventricle.

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TABLE II Results of Total 12-Lead QRS Voltage Criterion Left Ventricular Mass Index (several cutoff points)

ECG Criteria — QRS 12 Leads (mm)	Patients with: LVH+ (n = 60)	LVH− (n = 14)	Sensitivity	Specificity	Accuracy
>175	13	3	0.28	0.89	0.51
>170	14	3	0.23	0.79	0.34
>165	15	5	0.25	0.64	0.32
>160	16	5	0.27	0.64	0.34
>155	21	7	0.35	0.50	0.38
>150	21	7	0.35	0.50	0.38
>145	24	8	0.40	0.43	0.41
>140	26	8	0.43	0.43	0.43
>135	29	10	0.48	0.29	0.45
>130	30	13	0.50	0.07	0.42
>125	33	13	0.55	0.07	0.46
>120	37	13	0.62	0.07	0.51
>115	39	14	0.65	0	0.46
>110	41	14	0.68	0	0.55

ECG = electrocardiographic; LVH = left ventricular hypertrophy.

tients (27 men and 47 women, mean age ± standard deviation 49 ± 11 years), LV mass >250 g was found in 46 (62%). Sixty patients (81%) had LV mass index greater than normal. LV mass was 258 ± 95 g, and LV mass index was 170 ± 57 g/m² (men) and 141 ± 47 g/m² (women). The sensitivity, specificity and accuracy of each cutoff point studied in the total 12-lead voltage are listed in Tables I and II (LV mass index). A total 12-lead voltage >120 mm shows a good sensitivity and the best accuracy with both criteria for LV hypertrophy. The sensitivity, specificity and accuracy of each cutoff point are higher when one considers LV mass >215 g as LV hypertrophy, perhaps because this is a more restrictive criterion. Table III summarizes the results obtained with total 12-lead voltage >120 mm and other electrocardiographic criteria of LV hypertrophy previously studied in these patients.[6] The correlation coefficient between LV mass and the total 12-lead QRS voltage was 0.449 ($p < 0.05$). The regression equation was: LV mass = 105 + 1.09 total 12-lead QRS voltage ($p < 0.01$).

TABLE III Comparison of Different Electrocardiographic Criteria of Left Ventricular Hypertrophy in Systemic Hypertension

ECG Criteria	Sensitivity	Specificity	Accuracy
RaVL >11 mm	0.11	0.93	0.42
RV5–V6 + SV1 >35 mm	0.17	0.93	0.46
Largest R + S >45 mm	0.06	1	0.42
R–E score >=5	0.11	1	0.45
RV6:RV5 >0.65	0.89	0.21	0.64
Total QRS >120 mm	0.80	0.54	0.70

ECG = electrocardiographic; Largest R + S = largest R wave plus largest S wave in precordial leads (10 mm = 1 mV); RaVL = R-wave amplitude in lead aVL (10 mm = 1 mV); R–E score = Romhilt-Estes point score system; RV5–V6 + SV1 = R-wave amplitude in leads V_5 or V_6 (the largest) plus S-wave amplitude in lead V_1 (10 mm = 1 mV); RV6:RV5 = ratio between R-wave voltage of leads V_6 and V_5; Total QRS = total QRS voltage from all 12 electrocardiographic leads (10 mm = 1 mV).

This study is the first to examine total 12-lead voltage in patients with essential hypertension. A total 12-lead QRS voltage >120 mm is a good electrocardiographic criterion of LV hypertrophy, given its good sensitivity (0.80) and accuracy (0.70). A total 12-lead QRS voltage >120 mm is a better criterion than those most frequently used, as we have shown recently in the same patients.[6] Measurement of total 12-lead QRS voltage provides a sensitive index of LV hypertrophy among patients with essential hypertension and gives a relatively reasonable estimation of LV mass in a disease in which cardiac hypertrophy has independent prognostic significance.

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Transesophageal Echocardiographic Assessment of Congenital Coronary Artery to Coronary Sinus Fistulas in Adults

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Coronary artery to coronary sinus fistula is a rare congenital disorder. Aortography and selective coronary angiography are currently the diagnostic modes of choice for the evaluation of congenital coronary artery fistulas, but recent reports have demonstrated the usefulness of noninvasive techniques.[1-3] We describe 3 patients in whom the relatively new technique of transesophageal echocardiography was found useful not only in the diagnosis and precise localization of these lesions but also in the intraoperative evaluation of the surgical repair (Table I, Figures 1 to 3).

All transthoracic 2-dimensional and color Doppler examinations were done in the standard manner using a commercially available system and a 2.0 or 2.5 MHz transducer.[4] Intraoperative transesophageal echocardiographic studies were also performed in the standard manner[5] using a 5 MHz transducer (Hewlett-Packard 77760A system for patients 1 and 2 and Aloka 870 biplane system for patient 3). The proximal coronary arteries were examined using the standard basal short-axis view[6] and the coronary sinus outlined in the right ventricular inflow plane.

Clinically, patient 1 presented with episodes of atrial flutter, patient 2 had frequent ventricular ectopics and patient 3 had non-anginal chest pain. Transesophageal echocardiography correctly diagnosed fistulous connection into the coronary sinus near its opening into the right atrium from the right coronary artery in patient 1 and the left circumflex artery in patient 2. It also correctly delineated fistulous connection between the left circumflex artery and the coronary sinus near the left atrial appendage. In contrast, coronary angiography correctly diagnosed the fistulous site only in patient 1. In patient 2, the fistulous site was misdiagnosed as the low posterior right atrium, whereas in patient 3 the precise site of fistula into the coronary sinus could not be identified.

Coronary artery fistulas involve the right coronary artery in 50 to 55% of patients, the left coronary artery in 35%, and both coronary arteries in 5%. Low pressure structures are the most common recipient sites and include the right ventricle (40%), right atrium (25%), pulmonary artery (15 to 20%), coronary sinus (7%) and the superior vena cava (1%).[2] Coronary artery dilatation is usual and the degree of dilatation depends on the shunt size. In our patients, the involved coronary arteries were markedly dilated and tortuous in appearance, although the shunts were small. These shunts are usually <2:1.[7] Most patients are asymptomatic although angina (7%) and myocardial infarction (3%)[8] occur and are attributed to the coronary artery "steal" phenomenon. Congestive heart failure occurs in as many as 53% of patients with fistulous connections to the coronary sinus or right atrium,[9] although none of the current study patients had objective signs of heart failure. Fistula recurrence is rare[8] and occurred in the second patient of this report. When the coronary fistula drains into an atrium or the coronary sinus, atrial fibrillation is a sign of decompensation.[7] Only the first patient had atrial arrhythmias; the second had ventricular ectopics.

Transthoracic Doppler echocardiography has been used to detect and estimate flow velocities in coronary artery fistulas.[10] A meticulous examination is essential to

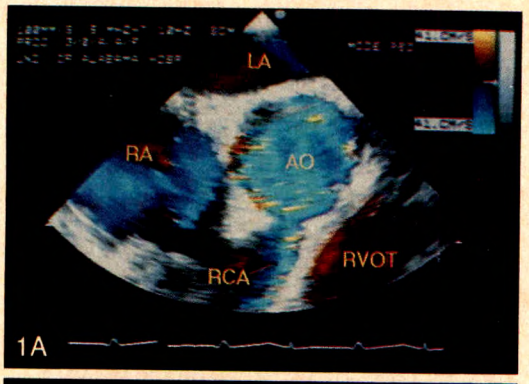
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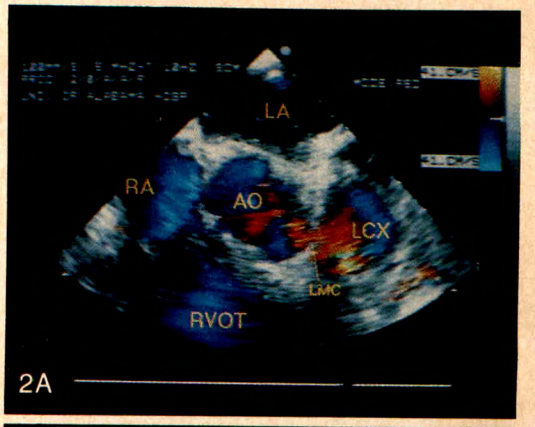
TABLE I Coronary Artery to Coronary Sinus Fistula

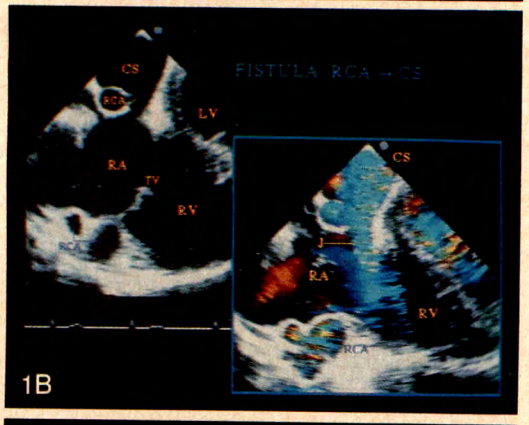
Pt.	Age (yr) & Sex	Magnitude L → R Shunt (cath)	Dilatation of Coronary Arteries *				Dilated CS*	Fistulous Connection (surgery)
			Right	LM	LAD	LC		
1	46M	1.1:1	+				+	RCA → CS (near opening into RA)
2	35F	1.3:1		+		+	+	LC → CS (near opening into RA)
3	53F	1.2:1		+		+	+	LC → CS (2 cm from LA appendage)

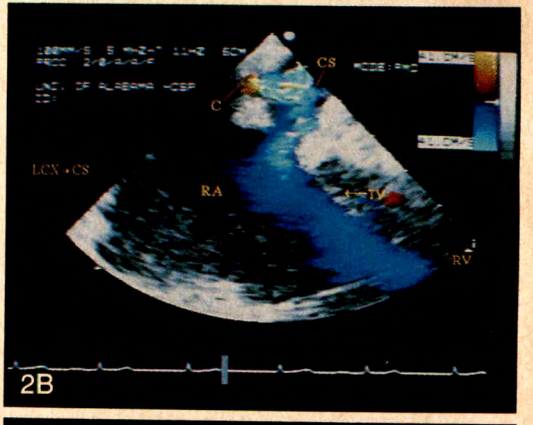
*Both by transesophageal echocardiography and angiography.
cath = cardiac catheterization; CS = coronary sinus; L → R Shunt = left-to-right shunt; LA = left atrium; LAD = left anterior descending; LC = left circumflex; LM = left main; RA = right atrium; + = present.

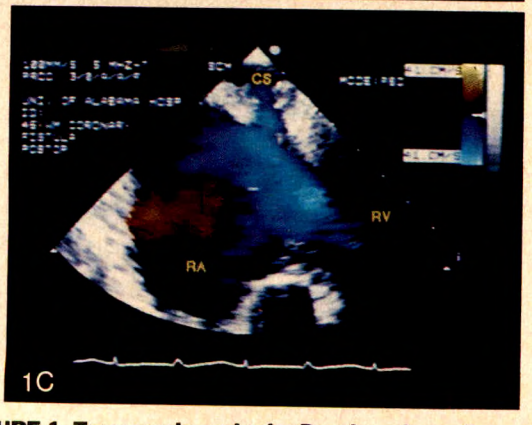
detect arteriovenous fistulas and is more difficult with a poor acoustic window. Also, transthoracic color Doppler echocardiography may not detect flow in the distal site of the coronary artery fistula.[10] In our patients, transthoracic echocardiography demonstrated dilated proximal coronary arteries and coronary sinus, but the fistulous connection was not identified in any patient. Coronary angiography has traditionally been used to diagnose coronary artery fistulas, but is invasive, and accurate local-











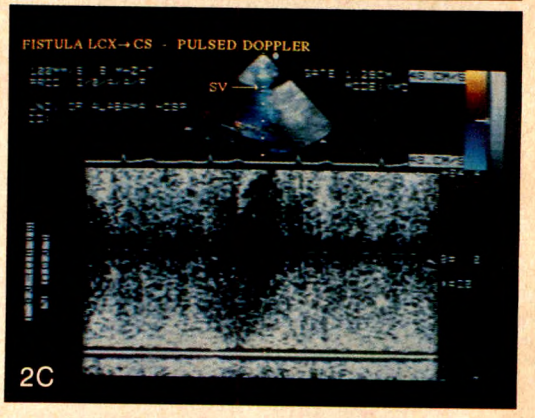
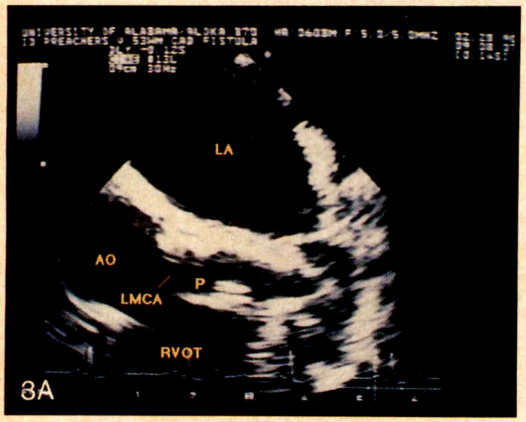


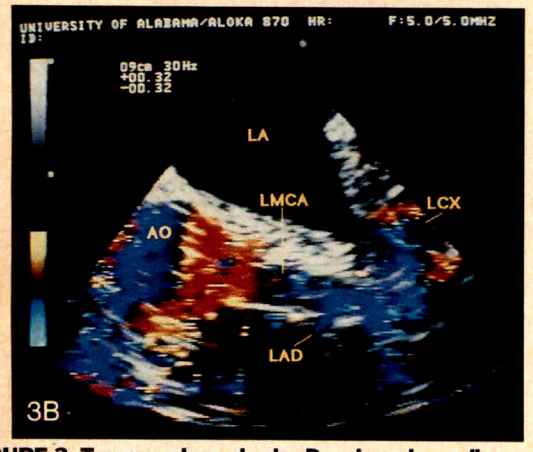
FIGURE 1. Transesophageal color Doppler echocardiogram in right coronary artery to coronary sinus fistula (patient 1). *A*, the aortic short-axis view demonstrates a markedly enlarged right coronary artery (RCA, lumen width = 20 mm) with mosaic-colored flow signals within it and in the aortic root (AO) indicative of turbulent blood flow. *B*, the right ventricular inflow view demonstrates several large, bounded echo free spaces containing mosaic-colored signals indicating turbulent blood flow. These structures represent segments of the enlarged and tortuous right coronary artery viewed in the long-, short- and oblique-axis planes. Mosaic flow signals from 1 of these structures are seen moving through an area of discontinuity into the grossly enlarged adjacent coronary sinus, near its entrance into the right atrium. *C*, after surgical obliteration of the fistulous connection, mosaic-colored flow signals in the coronary sinus (CS) are replaced by blue signals indicative of laminar flow. J = jet from coronary sinus entering the right atrium; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

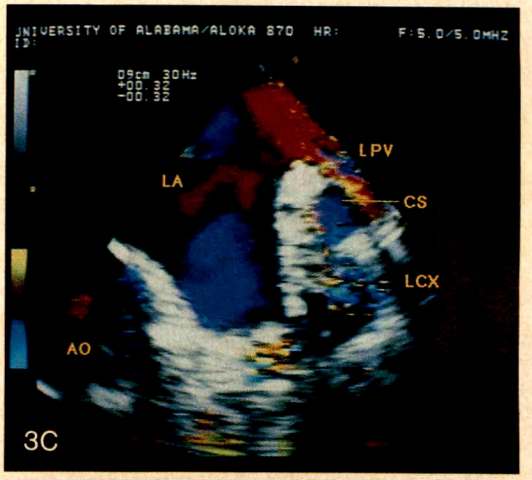
FIGURE 2. Transesophageal color Doppler echocardiogram in a patient with a left circumflex coronary artery to coronary sinus fistula (patient 2). *A*, the aortic (AO) short-axis view demonstrates enlargement of the left main (LMC) and circumflex (LCX, lumen width = 16 mm) coronary arteries. *B*, mosaic-colored signals indicative of turbulent blood flow are seen moving from the left circumflex coronary artery into the coronary sinus (CS), near its entrance into the right atrium (RA). Large circular and linear bounded spaces were also noted in this patient adjacent to the coronary sinus and represented the enlarged and tortuous LCX segments viewed in long- and short-axis. *C*, color Doppler-guided pulsed Doppler interrogation of the communication site demonstrates aliased high-velocity signals throughout the cardiac cycle. C = communication; LA = left atrium; OT = outflow tract; RV = right ventricle; SV = pulsed Doppler sample volume; TV = tricuspid valve.

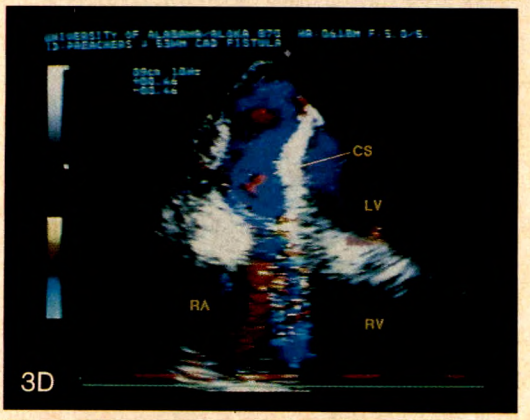
ization of the communication site may not be possible.[11] Transesophageal echocardiographic acoustic windows allow superior imaging of the cardiac structures[5] and hence would be expected to more reliably assess these anomalies than the transthoracic technique. One previously reported case was diagnosed by transesophageal color Doppler echocardiography,[3] but it was evident on careful perusal of the content and illustrations of that report that the precise site of the fistulous communication was not identified.

Transesophageal echocardiographic detection of a dilated coronary artery in an adult should raise the suspicion of a coronary artery fistula in the absence of a prior percutaneous angioplasty of the involved artery or a history of Kawasaki's disease. Associated dilatation of the coronary sinus further raises the suspicion of a fistulous communication between the two, especially if other causes of coronary sinus dilatation, such as a left-sided superior vena cava, an anomalous pulmonary venous connection to the coronary sinus, or marked right heart enlargement, are excluded by echocardiography. In these patients, a meticulous transesophageal echocardiographic examination using standard and nonstandard planes (including the right ventricular inflow view as well as examination of the coronary sinus near the left atrial appendage, and following as much of the course of the dilated coronary artery and the coronary sinus[11] as possible) should prove helpful in delineating the fistulous connection. Exact anatomic localization of the fistulous connection assists the surgeon in deciding the surgical approach as well as in obliterating the site of fistula.[12] As









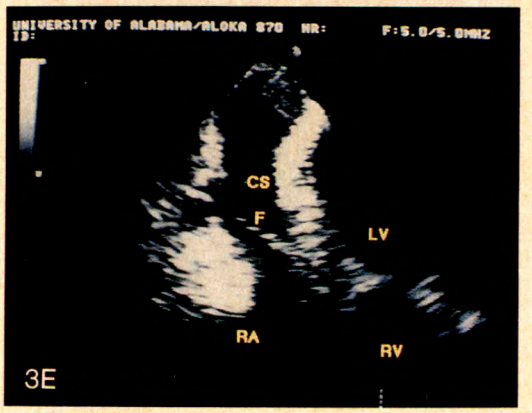


FIGURE 3. Transesophageal color Doppler echocardiogram in a patient with a left circumflex coronary artery (CA) to coronary sinus fistula (patient 3). *A* and *B*, the aortic (AO) short-axis view demonstrates marked enlargement of the left circumflex (LCX, lumen width = 13 mm) CA. There is also enlargement of the left main CA (LMCA, lumen width = 12 mm) with a prominent atherosclerotic plaque (P) noted within its lumen. *C*, the left circumflex CA is shown communicating with another structure, located in the usual position of the coronary sinus (CS) in this plane and adjacent to a left-sided pulmonary vein (LPV). *D* and *E*, after surgical obliteration of the fistula, mosaic-colored turbulent flow signals within the coronary sinus are replaced by laminar flow signals *(blue)*, except at its entrance into the right atrium (RA), where the fenestrated (F) Thebesian valve results in persistence of turbulent blood flow. LA = left atrium; LAD = left anterior descending CA; LV = left ventricle; OT = outflow tract; RV = right ventricle.

demonstrated in 2 of the 3 patients in the current study (patients 2 and 3), the exact site of the fistulous connection may not be delineated by angiography and in this regard transesophageal echocardiography appears to be a valuable supplement to this invasive technique. In the current study, the fistulous sites were accurately identified and localized preoperatively in each of the 3 patients by transesophageal 2-dimensional and color Doppler echocardiography. The involved dilated coronary arteries were also identified. These findings in the patients in the current study were all confirmed at surgery. In our patient series, transesophageal echocardiography was also found useful after surgery in confirming successful closure of the fistula. After surgical obliteration of the fistula, the fistulous connection between the coronary artery and the coronary sinus could no longer be demonstrated in any of the 3 patients. In addition, the flow signals in both the coronary sinus and the involved coronary artery no longer appeared mosaic-colored, indicating the absence of turbulent blood flow. In patient 3 the mosaic-colored signals persisting in the region of the coronary sinus entrance into the right atrium after surgical repair were related to the fenestrated Thebesian valve noted by transesophageal echocardiography and at surgery.

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Postprandial Changes in Oxygen Saturation in Patients with Bidirectional Cavopulmonary Shunts

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The bidirectional cavopulmonary shunt, a modification of the Glenn shunt in which superior caval venous blood is diverted to both pulmonary arteries,[1] is being applied with increasing frequency as part of a staged approach to Fontan's operation.[2–4] In patients with bidirectional cavopulmonary shunts, inferior caval blood is directed to the systemic ventricle, and the degree of cyanosis exhibited by these patients is substantially dependent on the ratio of blood flow through the superior and inferior venae cavae. Because splanchnic (and thus inferior caval) venous flow increases during digestion of a meal, it seems reasonable that patients with bidirectional cavopulmonary shunts should exhibit some decrease in systemic arterial oxygen saturation during the postprandial period.

We studied 8 subjects with bidirectional cavopulmonary shunts (aged 2 to 24 years) and 8 control patients (aged 4 to 26 years) with no cardiac disease. The bidirectional cavopulmonary shunt group included all patients that we followed who had undergone this operation, but had not yet undergone complete Fontan repair as of November 1990 (Table I). Anterograde pulmonary blood flow was completely interrupted by congenital pulmonary atresia, division of the pulmonary trunk, or ligation of the pulmonary trunk (confirmed by cardiac catheterization or Doppler echocardiography). Subjects fasted ≥3 hours before the study. Systemic arterial saturation was measured by pulse oximetry (Biox 3700, Ohmeda, Boulder, Colorado) before and after consumption of a standard meal. Oxygen saturation was continuously recorded over 1- to 2-minute intervals (N-2 chart recorder, Gilson, Villiers le Bel, France), and baseline measurements were taken 30 minutes, 15 minutes, and immediately before the test meal. Oxygen saturation was again measured immediately after consumption of the test meal and at 15-minute intervals for the subsequent 2 hours. Mean baseline oxygen saturation was calculated for each subject, and the 9 postprandial measurements were divided into 3 consecutive segments of 3 measurements each, which were also averaged. Data were analyzed by repeated measures analysis of variance, and a p value <0.05 was statistically significant. A decrease in oxygen saturation of <5% was not considered clinically significant. The test meal consisted of ad libitum volume of Carnation Instant Breakfast Drink® mixed with whole milk, and subjects were required to consume ≥20% of daily caloric requirements based on body surface area. This protocol was approved by the University of Arizona Human Subjects Committee, and informed consent was obtained from all subjects or their parents.

Mean oxygen saturation in our patients with bidirectional cavopulmonary shunts was 77 ± 2% (mean ± standard error of the mean) in the fasted state. The response of oxygen saturation to the test meal in the control and bidirectional cavopulmonary shunt groups is plotted in Figure 1. No changes in saturation were observed in the control group, confirming the reproducibility of pulse oximetry measurement in our protocol. The cavopulmonary shunt group exhibited decreased oxygen saturation up to 75 minutes after the meal, with return to baseline saturation by 90

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TABLE I Bidirectional Cavopulmonary Shunt Group

Pt.	Age (yrs)	Mean Baseline Oxygen Saturation (%)	Mean Postprandial Oxygen Saturation (%)	Cardiac Diagnoses
1	6	81	82	DILV, L-MGA, int IVC
2	24	74	73	DILV, DORV, CAVO
3	4	81	80	DILV, pulmonary atresia
4	6	61	55	Tricuspid atresia*
5	2	80	78	Tricuspid atresia
6	5	79	78	Tricuspid atresia, TGA
7	4	80	76	Tricuspid atresia
8	4	79	78	Mitral atresia, DORV

*Hemidiaphragm paralysis.
CAVO = common atrioventricular valve orifice; DILV = double-inlet left ventricle; DORV = double-outlet right ventricle; int IVC = interrupted inferior vena cava with azygous continuation; L-MGA = L-malposition of the great arteries; TGA = transposition of the great arteries.

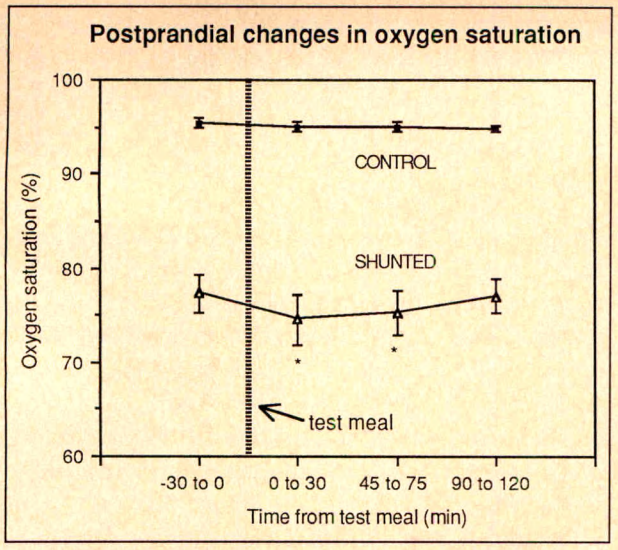


FIGURE 1. Mean oxygen saturation is plotted against time from the test meal in control subjects (CONTROL) and patients with bidirectional cavopulmonary shunts (SHUNTED). *Error bars* represent standard error of the mean. After meal consumption, oxygen saturation decreases mildly in the shunted group and returns to the fasting baseline by 90 minutes. *p <0.05 versus fasting.

minutes. Baseline oxygen saturation and mean postprandial saturation during the first 2 segments (0 to 75 minutes) are listed individually for the shunted patients in Table I. The mean magnitude of the decline (as percent saturation) was 2.4% (95% confidence limits 0.9 to 4.0%), which was statistically significant ($p < 0.01$), but not clinically significant.

Decreased arterial oxygen saturation in the bidirectional cavopulmonary shunt group could have been caused by an increase in the ratio of inferior to superior vena cava blood flow, by a decrease in inferior vena cava oxygen saturation, or by both mechanisms. Splanchnic blood flow increases during digestion of a meal, and this increase can persist as long as 4 to 6 hours.[5] Our test meal was designed to produce a rapid and significant increase in splanchnic blood flow. We used a liquid meal to promote rapid gastric emptying and rapid onset of increased splanchnic blood flow, and the meal contained substantial amounts of fat and protein (26% and 21% of calories, respectively) to ensure an increase of reasonable magnitude. The relatively short duration (<90 minutes) of reduced oxygen saturation may have been due to the liquid nature of our test meal, but the magnitude of the reduction should be representative of mixed meals with substantial protein and fat content.

On a theoretic basis, decreased systemic arterial oxygen saturation after meal consumption in patients with bidirectional cavopulmonary shunts was clearly expected, but the magnitude of this decrease was not clear. The mean decrease in oxygen saturation was 2.4%, but owing to the limited number of patients available for this study the 95% confidence limits of this decrease were 0.9 to 4.0%. Study of a larger number of patients would probably have yielded a narrower confidence interval. We also included patients regardless of age, and it is possible that the magnitude of the postprandial response may vary in patients of different age groups. Nevertheless, we have demonstrated a statistically significant but clinically trivial postprandial decrease in oxygen saturation in our patients. This phenomenon should not, therefore, be an impediment to application of the bidirectional cavopulmonary shunt in appropriate cases. We speculate that similar studies of postprandial oxygen saturation in infants with bidirectional cavopulmonary shunts or in patients with systemic-to-pulmonary arterial shunts would also yield important clinical information.

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Right-Sided Valve Regurgitation in Congenital Heart Disease Determined by Doppler Regurgitant Velocity Measurement

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Using echo-Doppler it is possible to estimate the systolic (in absence of right ventricular outflow obstruction) and end-diastolic pulmonary artery (PA) pressure noninvasively by applying the modified Bernoulli equation on tricuspid and pulmonary regurgitant flow velocity, respectively.[1,2] Application of this method is limited by the necessity of presence of tricuspid or pulmonary regurgitation (TR, PR) and the ability to measure the regurgitant velocity adequately. The prevalence of Doppler determined TR and PR in children with congenital heart disease, especially in respect to the proportion of right-sided regurgitation useful in obtaining noninvasive PA pressure estimates is not very well known. We determined the prevalence of TR and PR in children seen at a pediatric cardiology outpatient clinic with respect to the Doppler applicability in noninvasively estimating PA pressure.

Study participants were 272 consecutive patients (154 male and 118 female patients) admitted to our pediatric echocardiography outpatient clinic. Median age was 5.6 years (range 0 to 20). Congenital heart disease was present in 229 patients, whereas 43 (16%) had a structurally normal heart (Table I). Of those with heart disease, 73 (32%) had had cardiac intervention such as surgery or balloon valvuloplasty. All patients had sinus rhythm, 20 had right bundle branch block.

All patients lying in the left lateral recumbent position and quietly breathing were screened on the presence of right-sided regurgitation using color-coded Doppler (Toshiba SSH-65A equipped with a 2.5-MHz and 3.75-MHz Duplex transducer). Color-coded Doppler settings were standardized: a pulse repetition frequency of 4 KHz allowing measurement of flow velocity up to 0.54 m/s (3.75-MHz transducer) or 0.75 m/s (2.5-MHz transducer) was routinely used. Color gain was set at a level at which static background noise barely appeared. If estimated jet length exceeded 1 cm, we tried to measure the regurgitant velocity using combined color-coded and continuous-wave echo-Doppler (3.0 MHz, filter 1,600 Hz).

TR was separated by 2 observers into 3 classes: 0-no regurgitation; I-regurgitation; but not meeting criteria of class II; and II-holosystolic regurgitation with regurgitant jet length >1 cm and well-enveloped Doppler spectrum.

PR was classified in a similar way as: 0-no regurgitation; I-regurgitation, but not meeting criteria of class II, including regurgitation after (partial) valvectomy; and II-holodiastolic regurgitation with jet

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TABLE I Prevalence of Pulmonary and Tricuspid Regurgitation According to Diagnosis

		PR		TR		PR and TR			
Diagnosis	No. of Pts.	I	II	I	II	A	B	C	D
VSD	21	4	0	6	0	0	0	4	3
ASD	18	1	1	6	0	0	0	0	4
PDA	5	0	1	1	0	0	0	1	0
PS	30	5	3	4	0	2	3	3	2
AS	24	3	3	4	0	1	0	5	2
AS/AR	27	10	3	2	0	0	0	5	2
Coarctation	6	0	2	1	0	0	0	1	2
Coarctation/AS	6	0	1	1	0	0	0	0	2
AVSD	7	0	0	2	1	0	0	1	0
TF	17	1	0	1	0	0	3	0	8
TGA	9	0	1	3	0	0	0	0	1
Marfan	16	1	4	2	0	1	0	5	2
Complex	14	2	0	4	0	0	0	0	0
Other	29	4	0	2	3	2	0	5	2
Normal	43	4	5	6	0	1	0	6	4
Total	272	35	24	45	4	7	6	36	34
%	100	13	9	17	1	3	2	13	12

A = PR + TR both class II; AR = aortic regurgitation; AS = aortic stenosis; ASD = atrium septum defect; AVSD = atrioventricular septum defect; B = PR class I and TR class II; C = PR class II and TR class I; D = PR + TR both class I. PDA = persistent ductus arteriosus; PR = pulmonary valve regurgitation; PS = pulmonary regurgitation; TF = tetralogy of Fallot; TGA = transposition of the great arteries; TR = tricuspid regurgitation; VSD = ventricular septal defect.

length >1 cm and well enveloped end-diastolic Doppler spectrum. Class II regurgitation is assumed to be useful for PA pressure estimation. This study was approved by the local committee on human experimental research. Parental informed consent was obtained. Data are presented as median and range. Chi-square statistics were used in analyzing the association of prevalence of valvular regurgitation with sex, history of intervention and presence of right bundle branch block. Wilcoxon's 2-sample test was used to evaluate differences in age between the groups with and without regurgitation. Level of significance was set at 0.05.

Using combined color-coded and continuous-wave Doppler a high prevalence of right-sided valvular regurgitation, even in apparently normal patients was found. In Table I the distribution of the different classes of regurgitation is shown. Peak systolic TR velocity was 2.75 ± 0.46 m/s (mean ± standard deviation) and end-diastolic PR velocity, measured at the beginning of the Q-wave of the electrocardiogram, amounted to 1.10 ± 0.24 m/s. Patients with regurgitation were older than patients without it: In those with PR (class I and II) age was 9.9 years (range 0.6 to 19), whereas in the group without PR age was 2.7 years (range 0 to 20) ($p < 0.001$). Patients with TR (class I and II) were aged 8.8 years (range 0.1 to 19.2) and those without TR were 4.1 years (range 0 to 20) ($p < 0.001$). Of the 43 normal patients, those with regurgitation were older than those without it. No overall association of the prevalence of TR or PR with cardiac intervention or sex was found, but the prevalence of TR and PR was higher in those with right bundle branch block ($p < 0.05$). When all patients were divided into groups with and without class II regurgitation (class 0 and I), class II regurgitation was found to be more prevalent after intervention for both TR and PR (chi-square, $p < 0.001$).

In our young patient group in which we did not measure PA pressure invasively, class II PR was present in 25% and class II TR in only 6%. Currie et al[1] was able to use TR velocities in predicting right ventricular systolic pressure in 57% of patients (predominantly adults) with normal right ventricular pressure. Hamer[3] and Berger[4] and their co-workers measured TR velocity adequately in only 19 and 10% of such (adult) patients in contrast to 80% of those with elevated right ventricular pressure. Using PR end-diastolic velocity, Masuyama et al[2] found an analyzable PR in 86% of patients (aged 8 to 78 years) with and in 54% without pulmonary hypertension. The higher age, the use of more sensitive and smaller non-imaging transducers facilitating better alignment of the ultrasound beam with flow in the studies mentioned[1–4] might be an explanation for the relatively low prevalence of regurgitation useful for PA pressure assessment in this study. Furthermore, our definition of regurgitation that is useful for pressure estimation is probably more precise than in other investigations.

In apparently normal adults, a prevalence of regurgitation at both right-sided valves increasing with higher age has been reported,[5] whereas other investigators found a decreasing prevalence[6] with higher age. In this study concerning only infants and children, we found an increasing prevalence of TR and PR with increasing age in both diseased and normal children. Prevalence of class II regurgitation that is useful for estimating PA pressure also increased. Despite the better echocardiographic window in children especially in visualizing the pulmonary valve, TR and PR (in which the regurgitant velocity can be measured adequately) appears to be less prevalent in children than in adults.

Thus, the frequency of right-sided regurgitation in children with congenital heart disease and in normal subjects is high. The prevalence increases with age. However, class II regurgitation is much less prevalent, implying that a noninvasive estimation of PA pressure by using right-sided regurgitant velocities cannot be obtained very often in the younger age group.

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Transesophageal Echocardiographic Features of the Atrial Septum in Constrictive Pericarditis

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In constrictive pericarditis the heart is confined inside a rigid, noncompliant pericardium that limits ventricular and atrial distensibility in mid- and late diastole.[1] Reciprocity in ventricular filling during the respiratory cycle is the most characteristic finding in constrictive pericarditis.[2] Ventricular and atrial septal motion reflects instantaneous pressure differences between the right and left ventricle and the right and left atria, respectively. A characteristic M-mode finding in patients with constrictive pericarditis is the respiration-related displacement of the interventricular septum[2] (Figure 1). The motion of the atrial septum in constrictive pericarditis has not been well studied. Imaging of this structure with transthoracic echocardiography is limited. Transesophageal echocardiographic imaging of the atrial septum is particularly advantageous because the esophageal transducer faces this structure nearly perpendicular at a short distance.[3] The purpose of this report was to analyze the transesophageal echocardiographic motion of the atrial septum and its possible diagnostic value in constrictive pericarditis.

The study group consisted of 7 patients (3 women and 4 men, aged from 58 to 82 years) with clinical, echocardiographic and cardiac catheterization signs of constrictive pericarditis; in 2 cases the diagnosis was confirmed at operation; 3 patients had pericardial calcification seen at x-ray; 3 patients had sinus rhythm and 4 were in atrial fibrillation. The constriction was caused by tuberculosis in 3 patients: idiopathic in 2, postsurgical in 1 and secondary to malignant fibrous histiocytoma in 1. Every patient underwent transesophageal echocardiographic imaging of the atrial septum. For comparison, 10 patients of similar age, 5 in sinus rhythm and 5 with atrial fibrillation who underwent a transesophageal echocardiographic study for other reasons provide a control group.

Transesophageal echocardiography was performed using a commercially available Toshiba SSH-160 echocardiograph machine interfaced with a 5-MHz transducer, mounted on a flexible endoscope. After giving 3 to 5 mg of intravenous diazepam, 25 to 50 mg of intravenous meperidine, and topically anesthetizing the posterior pharynx with 10% xylocaine spray, the transesophageal probe was introduced in the esophagus and positioned posterior to the left atrium. A comprehensive sequence of transducer positions and tomographic sections were performed as has been described by the Mayo Clinic group.[3] At a distance of 35 cm from the patient's teeth, the left and right atrium and atrial septum were identified by clockwise rotation of the endoscope. Visualization of the membranous portion of fossa ovalis was always achieved. M-mode recordings of fossa ovalis were available from the real-time echogram to facilitate analysis of interatrial septal motion during the different phases of cardiac and respiratory cycles. Images were recorded in continuous loop, permitting frame-by-frame review. Imaging and recording time averaged 15 to 30 minutes per patient.

In the control group of patients, the atrial septum was curved slightly toward the right atrium during ventricular systole, and showed a minimal oscillation during atrial systole; respiration had little effect on its motion. In the group of patients with constrictive pericarditis a more marked curvature of the atrial septum during early diastole toward the right atrium was

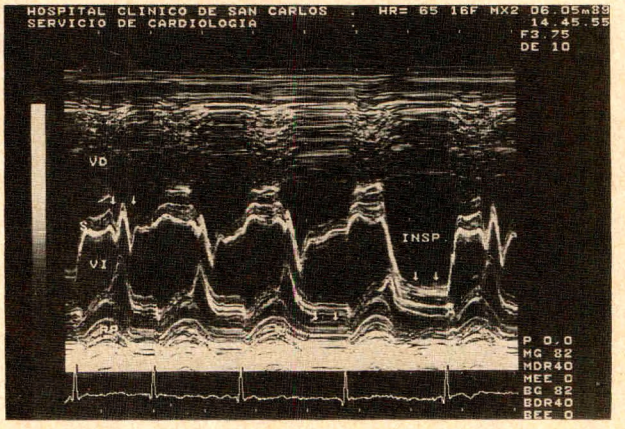


FIGURE 1. M-mode echocardiogram of a patient with constrictive pericarditis. A displacement of the ventricular septum toward the left ventricle during inspiration can be seen from the transthoracic echocardiographic approach. INSP. = inspiration; PP = left ventricular posterior wall; S = ventricular septum; VD = right ventricle; VI = left ventricle.

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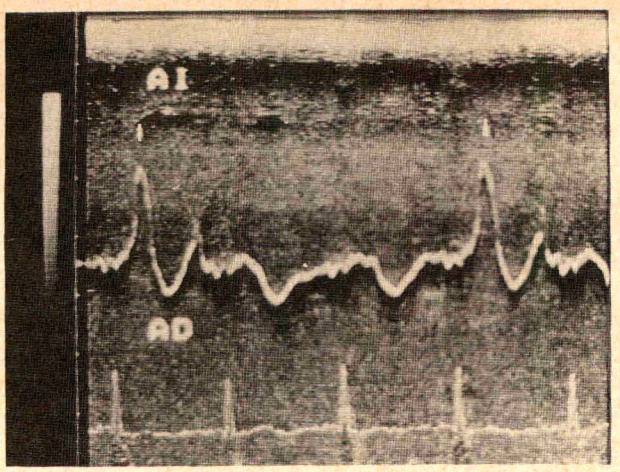


FIGURE 2. Transesophageal echocardiography. M-mode echocardiogram of the atrial septum in a patient with constrictive pericarditis that demonstrates a brisk motion toward the left atrium (AI) during inspiration (I). AD = right atrium.

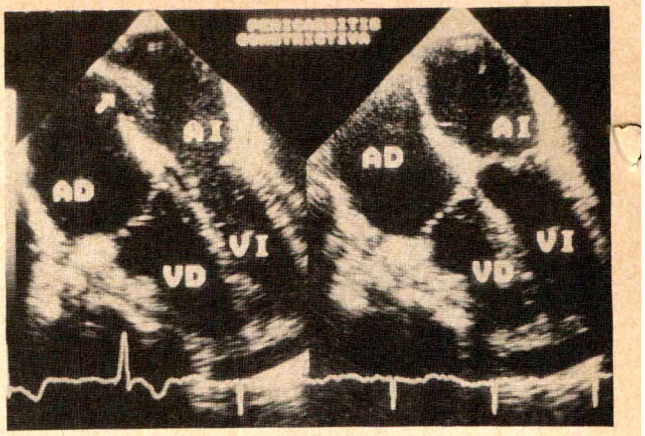


FIGURE 3. Tranesophageal echocardiography. Two-dimensional echocardiogram, 4-chamber view of a patient with constrictive pericarditis. Notice the displacement of the atrial septum *(arrow)* toward the left atrium (AI) during inspiration *(left image)*. AD = right atrium; VD = right ventricle; VI = left ventricle.

noticed. The motion of the atrial septum during atrial systole was similar to the control group, and the most remarkable finding was a brisk displacement of the atrial septum toward the left atrium during inspiration (Figures 2 and 3). This sign was present in all 7 patients with constrictive pericarditis and was absent in the control group.

To establish the mechanism of this anomalous atrial septal motion, simultaneous pressure tracings of pulmonary wedge and right atrium were registered in 3 patients with a marked decrease of pulmonary wedge pressure during inspiration, whereas right atrial pressure remained unchanged (Figure 4).

In constrictive pericarditis the scarred and rigid pericardium will lead to a similar pressure volume relation within the heart chambers. Therefore, a change in volume in 1 chamber affects both the pressure and volume in the other chambers. This particular motion of the very compliant atrial septum reflects instantaneous differences in pressure between the right and left atria. In constrictive pericarditis the heart is encased in a noncompliant pericardium that insulates it from fluctuations in intrathoracic pressure. With inspiration, the intrathoracic pressure and thus pulmonary venous pressure and left atrial pressure decreases, but the right atrial pressure remains high. This pressure difference between the atrial chambers will shift the atrial septum toward the left atrium. Transesophageal echocardiographic visualization of the atrial septum is practically always achieved; therefore, the aforementioned motion will be easily identified by this technique. The analysis of the atrial septal motion has been studied by different investigators,[4–8] but as far as we know this abnormal atrial septal motion in constrictive epicarditis has not been previously de-

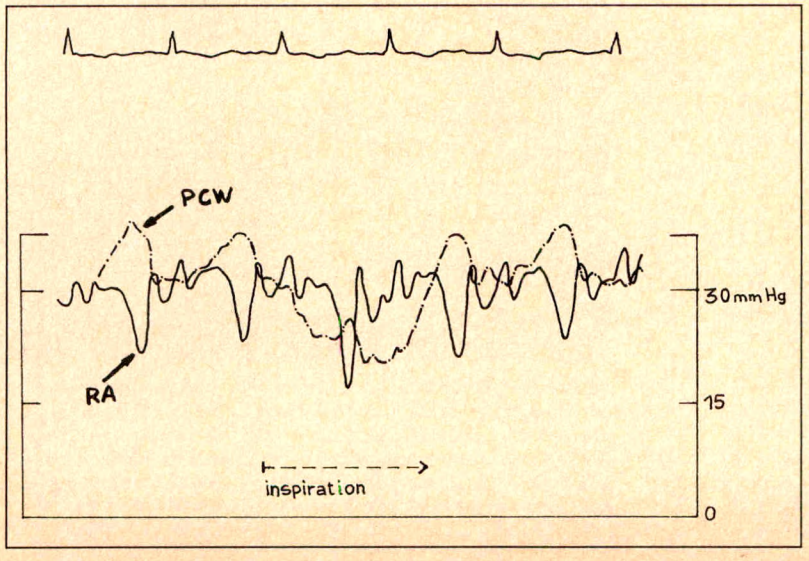


FIGURE 4. Tracings of pulmonary wedge (PCW) and right atrial (RA) pressures recorded from a patient with constrictive pericarditis that demonstrate a decrease in pulmonary wedge pressure during inspiration.

scribed. It is worthwhile to mention that this sign was absent in 2 patients with amyloid cardiomyopathy not described here.

The present report suggests that the atrial septal motion described is a fairly consistent echocardiographic finding in constrictive pericarditis and may be useful in the assessment of this entity. This assumption, however, is based on a small number of patients.

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Acute Myocardial Infarction Due to Thrombolytic Reperfusion of Chronically Occluded Saphenous Vein Coronary Bypass Grafts

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Late occlusion of saphenous vein grafts is a major cause of recurrent angina in the years after successful coronary artery bypass surgery. Reestablishment of circulation to the involved artery is problematic, because direct angioplasty may be precluded by chronic occlusion of the native artery and extensive thrombus in the occluded vein graft. It has recently been demonstrated that chronically occluded aortocoronary saphenous vein grafts can be successfully recanalized by prolonged low-dose intragraft infusions of urokinase.[1–5] Hartmann et al[2] achieved recanalization in 11 of 12 chronically occluded grafts using 16- to 72-hour urokinase infusions in total doses ranging from 870,000 to 6,290,000 U. Marx et al[3] reported recanalization in 8 of 10 grafts with shorter urokinase infusions. Neither investigator reported significant cardiovascular complications as a result of the procedure. We report on 2 consecutive patients who developed acute myocardial infarction as a direct result of successful thrombolytic reperfusion of chronically occluded saphenous vein grafts.

CASE 1: *A 60-year-old man was asymptomatic until he developed a small non-Q-wave myocardial infarction 5 years after coronary bypass surgery. Coronary arteriography revealed total occlusion of the right coronary artery (as documented 5 years earlier) and total occlusion of the saphenous vein graft to the right coronary artery. All branches of the left coronary artery were either patent or perfused by normally functioning grafts. The patient was treated medically, but returned 3 weeks later with a new syndrome of lifestyle-limiting exertional angina. Repeat cardiac catheterization showed no interval change in coronary anatomy, and well developed collaterals from the left coronary to the occluded right coronary artery were noted. It was determined that the occluded right coronary was responsible for this patient's angina, and reperfusion with intragraft urokinase was recommended.*

A 6Fr A2-multipurpose guiding catheter was placed in the ostium of the vein graft and an infusion wire (0.038-inch Cragg Convertible®, Medi-tech Corporation, Watertown, Massachusetts) was inserted into the region of the distal anastomosis over a 0.014-inch guidewire. Urokinase was administered at a rate of 100,000 U/hour (50,000 U/hour through the proximal catheter and 50,000 U/hour through the distal infusion catheter). Intravenous heparin was administered as a 10,000-U initial bolus followed by 1,000 U/hour continuous infusion. One hour after initiating the urokinase infusion, the patient began to experience recurrent episodes of severe substernal chest pressure associated with inferior ST-segment elevation. The chest discomfort persisted in a waxing and waning pattern for 8 hours before eventually resolving. Enzymes confirmed acute myocardial infarction, with an increase in creatine kinase from normal levels to 958 U/liter with 4% MB fraction, and an increase in lactate dehydrogenase from normal levels to 451 U/liter with reversal of the 1:2 ratio. Follow-up angiography after 60 hours of urokinase infusion demonstrated patency of the saphenous vein graft, good flow into the grafted portion of the native right coronary, and no evidence of embolized thrombus in the distal right coronary artery. Echocardiography demonstrated worsening of the inferior left ventricular wall motion abnormality with development of inferoposterior dyskinesia, a decline in shortening fraction from 28 to 22%, and enlargement of the left ventricle. There was no interval change in the left coronary anatomy.

CASE 2: *A 68-year-old man was hospitalized with medically refractory angina 7 years after coronary bypass surgery. Acute myocardial infarction was ruled out and coronary arteriography was performed. Grafts to the left coronary artery were patent, whereas both the native right coronary and its saphenous vein bypass graft were totally occluded. Reperfusion of the right coronary vein graft was performed using the same urokinase infusion protocol previously described (see case 1).*

The patient experienced no symptoms during the 48-hour course of urokinase infusion. However, serial cardiac enzymes demonstrated acute myocardial infarction on the first day of infusion, with an increase in creatine kinase from normal levels to 783 U/liter with 7% MB, and a peak lactate dehydrogenase level of 399 U/liter with reversal of the 1:2 ratio. Angiography after 24 hours of infusion demonstrated patency of the graft, but residual thrombus within the body of the graft. Migration of partially lysed thrombus into the native vessel with obstruction of a distal branch was observed (Figure 1). Angiography after 48 hours of infusion demonstrated patency of the graft without residual thrombus. Nonsustained ventricular tachycardia oc-

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curred 48 hours after completion of the urokinase infusion.

We report 2 cases of acute myocardial infarction resulting directly from successful thrombolytic reperfusion of chronically occluded aortocoronary saphenous vein grafts. In both cases, patients had exertional angina due to inadequate collateral perfusion of totally occluded coronary arteries. Existing collaterals were sufficient to prevent ischemia at rest and recent infarction was excluded in both cases before attempting recanalization. Thus, acute infarction was conclusively linked to thrombolytic reperfusion of the grafts despite prior adequacy of collateral flow. Both patients had clinical sequelae of infarction; ventricular enlargement in one and late ventricular arrhythmias in the other.

Acute myocardial infarction during vein graft reperfusion is most likely explained by recurrent embolization of thrombus into the native vessel. With successful reperfusion, flow into the distal right coronary artery may revert from a retrograde collateral pattern to a normal anterograde pattern. This would facilitate flow of thrombus into the small distal branches of the reperfused vessel, interrupting previously established collateral flow patterns as well as normal anterograde flow patterns. The large mass of thrombus in occluded grafts may provide the basis for recurrent embolization, with involvement of many different distal branches. Subsequent lysis of small emboli leaves no evidence of the mechanism of infarction at follow-up angiography. The clinical course of patient 1 with waxing and waning ischemia and patent vessels at follow-up angiography supports this hypothesis.

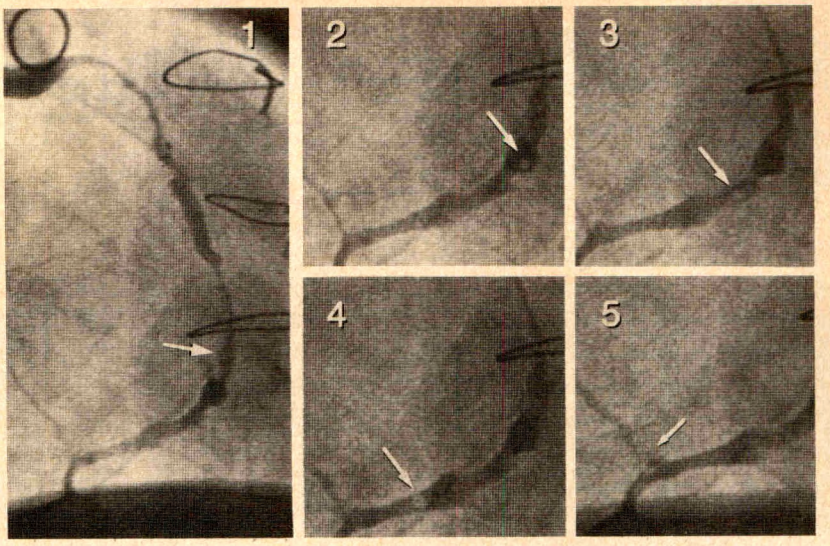


FIGURE 1. Arteriograms of saphenous vein graft of patient 2. *Arrows* indicate migration of partially lysed thrombus from the graft body to native right coronary, with obstruction of a branch vessel.

The incidence of acute myocardial infarction due to graft reperfusion is unknown. Our report of clinically silent infarction and occurrence in 2 consecutive patients indicates that this complication may occur frequently. There has been only 1 other report of a patient with evidence of acute myocardial infarction complicating urokinase infusion of a chronically occluded vein graft.[6] This was recognized by typical chest pain and ST-segment elevation.

We conclude that acute myocardial infarction is a potential complication of late thrombolytic reperfusion of occluded aortocoronary saphenous vein grafts. Because myocardial infarction may be clinically silent, close observation and monitoring of the electrocardiogram and cardiac enzymes must be performed whenever this procedure is undertaken. Acute myocardial infarction due to graft reperfusion may result in deterioration of left ventricular function and late ventricular arrhythmias. Until a prospective study to determine the incidence of this complication is completed, late thrombolytic reperfusion of chronically occluded saphenous vein bypass grafts should be considered only when more conservative therapeutic options have failed.

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Spontaneous Echo Contrast Effect as an Indicator of Flow-Limiting Coronary Stenosis

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Recent development of 2-dimensional intravascular ultrasound imaging allows the use of ultrasound to assess the status of native coronary arteries and bypass grafts in vivo. Previous investigators[1,2] have documented the compatibility of ultrasound, histology and angiography to assess percent stenosis. The case presented here demonstrates additional information that may be obtained from intravascular ultrasound imaging about blood flow.

The patient was a 67-year-old man who had undergone coronary artery bypass grafting 9 years previously. Because recurrent angina pectoris was crescendo in nature the patient underwent cardiac catheterization. At catheterization he was found to have a patent saphenous vein graft to the obtuse marginal branch of the left circumflex coronary artery; however, there was an 80% diameter stenosis at the anastomotic site. Runoff of angiographic contrast in the distal vessel was grade 3 based on the Thrombolysis in Myocardial Infarction trials.[3] Two-dimensional intravascular ultrasound imaging of the proximal saphenous vein graft was performed before and after balloon angioplasty of the stenosis, at the bypass graft anastomosis. A 30-MHz mechanical ultrasound system deployed by a 5Fr monorail catheter over a 0.014-inch guidewire was used (Cardiovascular Imaging Systems, Sunnyvale, California). After percutaneous transluminal coronary angioplasty the angiographic 80% diameter stenosis was reduced to 20%. Figure 1A demonstrates the intravascular ultrasound images obtained in the proximal left circumflex saphenous vein graft before dilatation of the distal stenosis. Note the intraluminal speckled pattern. Figure 1B is an ultrasound image of the same portion of the vessel under the same conditions (gain settings) after angioplasty. The vessel lumen is now free of the speckled appearance.

This case demonstrates a phenomenon that previously has not been described. We hypothesize that the speckled pattern is due to echo reflections from red blood cells, seen only when blood flow is impeded as in this case by a distal hemodynamically significant stenosis. Before and after balloon angioplasty of the distal lesion, angiographic runoff was brisk (grade 3) but the speckled appear-

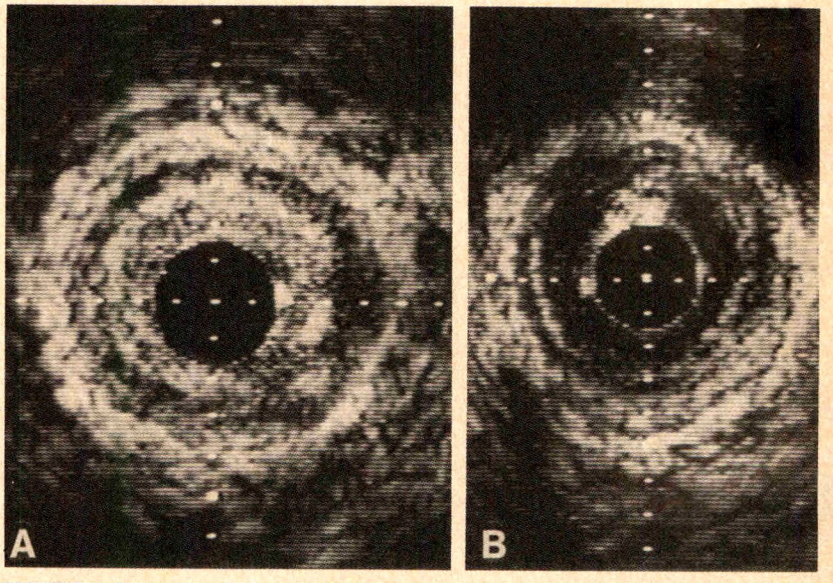


FIGURE 1. The image before angioplasty on the left *(A)* demonstrates a speckled intraluminal appearance that is not seen in the image after angioplasty *(B)*. Note the gain settings are similar.

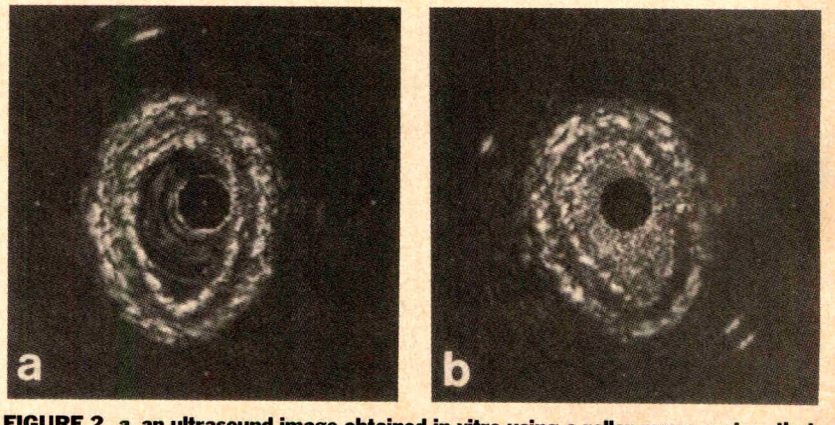


FIGURE 2. *a*, an ultrasound image obtained in vitro using a roller pump system that simulates flowing anticoagulated blood. Note the lumen is free of ultrasound signals. *b*, the same vessel imaged with nonflowing anticoagulated blood. Note that the speckled intraluminal signals.

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ance on ultrasound disappeared only after angioplasty. The high-frequency (30-MHz) intravascular ultrasound imaging catheters provide the resolution required to image red cells, but this only occurs when flow limitations exists.

To assess our hypothesis and in vivo human observations, we studied human arteries obtained at autopsy in an in vitro model. The arteries, which were of similar size to the saphenous vein graft (3.5 mm), were placed in a bath containing fresh anticoagulated blood (hematocrit 45%). The patient previously described had a hematocrit of 42%. Imaging was performed using the same ultrasound frequency (30 MHz) as that used in the in vivo studies. Figure 2A shows the in vitro image obtained during imaging in flowing blood simulated by use of a roller pump system. The clearly demarcated lumen is visible and there is absence of intraluminal reflections. Figure 2B shows the same vessel with imaging in nonflowing anticoagulated blood. The bright intraluminal speckled pattern is identical to that found in vivo in the saphenous vein bypass graft before angioplasty. This in vitro data support our concept that stagnant blood produces echogenic specular signals that can be detected by high-frequency ultrasound imaging catheters. Thus, the finding of this speckled pattern on intravascular ultrasound proximal to a stenosis may reflect the severity of a distal stenosis and imply a flow limitation. Furthermore, the resolution of this pattern after an intervention suggests improved distal flow and may be a useful guide to successful augmentation of blood flow.

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Nonsurgical Treatment of a Neonate with Pulmonary Atresia and Intact Ventricular Septum by Transcatheter Puncture and Balloon Dilation of the Atretic Valve Membrane

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Pulmonary atresia with intact ventricular septum remains one of the more difficult congenital cardiac defects to treat successfully, with low morbidity and mortality.[1,2] Balloon valvuloplasty has recently been shown to be effective in a staged approach to treatment of this lesion by further opening the valve membrane in patients who have had a limited surgical valvotomy.[3] This report describes our first patient treated by transcatheter perforation of the atretic valve membrane followed by balloon valvuloplasty.

A 5-hour-old 3.2-kg neonate was found to have echocardiographic features of pulmonary valve atresia or critical pulmonic stenosis, with a mildly hypoplastic but tripartite right ventricle, a small atrial septal defect and a patent ductus arteriosus. Prostaglandin E_1 was initiated to maintain patency of the ductus, and cardiac catheterization was undertaken to determine whether an opening in the valve membrane existed to allow balloon valvuloplasty by standard techniques. Figure 1 demonstrates absence of prograde pulmonary flow, but presence of a well-developed right ventricular outflow tract. The pulmonary valve membrane appeared thin and mobile on cineangiography.

A 5Fr preformed end-hole catheter (MP A-2, Cordis Corporation, Miami, Florida) could be manipulated to the outflow tract and positioned with the tip near the center of the valve membrane. Because the pulmonary artery above the outflow tract appeared to be relatively large, we elected to attempt transcatheter puncture of the membrane with a steerable 0.014-inch coronary guidewire. The soft end of the wire would not perforate the membrane even when the catheter tip was held firmly against the valve. Therefore, the stiff end was manually formed to approximate the curve of the outflow tract and was advanced approximately 2 mm past the end of the catheter as the catheter was held firmly against the valve membrane. Initially, the catheter tip moved away from the valve as the wire was advanced, but further pressure on the catheter as the wire tip was slightly extended resulted in puncture of the valve. The catheter was advanced to the level of the valve, but it would not pass through the valve membrane. Because of the potential for vessel perforation, the sharp stiff end of the guidewire was not advanced past the pulmonary artery bifurcation. Instead, the catheter was held

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in place against the valve membrane, and the wire was withdrawn. The soft end of the guidewire was then advanced with little difficulty back through the small opening in the membrane and manipulated to the right pulmonary artery.

Even a 4Fr catheter could not be advanced through the tiny opening in the valve membrane, so the soft end of the guidewire was carefully manipulated through the ductus and into the descending aorta. To gain control of the distal end of the guidewire, a snare was fashioned by folding a 0.014-inch coronary wire in half and forming the folded section into a "cobra-head" shape.[4] The previously placed umbilical artery catheter was exchanged over a guidewire for a 5Fr high-flow catheter (Ped Hi-Flo, USCI, Tewksbury, Massachusetts) with a lumen large enough to allow passage of the snare wire. The distal end of the transductal guidewire was grasped with the snare so that it could be held in place (Figure 1). By holding both ends of the guidewire firmly, it was possible to force a 4-mm coronary angioplasty catheter (Profile Plus, USCI) over the wire for an initial valvuloplasty. An 8-mm balloon valvuloplasty catheter (Proflex 5, Peripheral System Group, Mountain View, California) was then advanced over the wire through the enlarged opening and inflated twice to 8 atm (the pulmonary anulus was 5 mm). Pressure recordings after balloon dilation demonstrated pulmonary hypertension (in the presence of a large ductus) and no measurable gradient across the right ventricular outflow tract.

The patient tolerated the procedure well and prostaglandin E_1 was discontinued immediately after the catheterization. Echocardiography showed excellent prograde flow through the opened valve membrane; however, a small right ventricular cavity and continued right-to-left atrial shunting were seen. As the ductus closed over the next 24 hours, the patient remained asymptomatic, but systemic saturations fell into the 55% range by transcutaneous oximetry. The patient also developed mild abdominal distention, slight occult blood in the stools and questionable pneumatosis intestinalis. Because of concern that the relatively long procedure (2.8 hours) with catheter manipulation in the descending aorta could make the patient more susceptible to necrotizing enterocolitis, we elected to treat the patient conservatively, with 10 days of bowel rest and parenteral nutrition. Prostaglandin E_1 was restarted at a very low dose (0.01 μg/kg/min) and saturations remained in the 80 to 85% range. After 7 days, the prostaglandins were discontinued and the systemic saturation remained at 70 to 80%. Follow-up evaluation 2 months after the procedure showed normal growth of the patient and continued growth of the right ventricle. Saturation by oximetry was 82 to 85%. Echocardiography showed complete closure of the ductus, an estimated right ventricular pressure of 25 mm Hg, a pulmonary valve gradient of 15 mm Hg, and only mild tricuspid and pulmonary regurgitation.

This case illustrates a new technique that may make it possible to treat selected patients with pulmonary atresia and intact ventricular

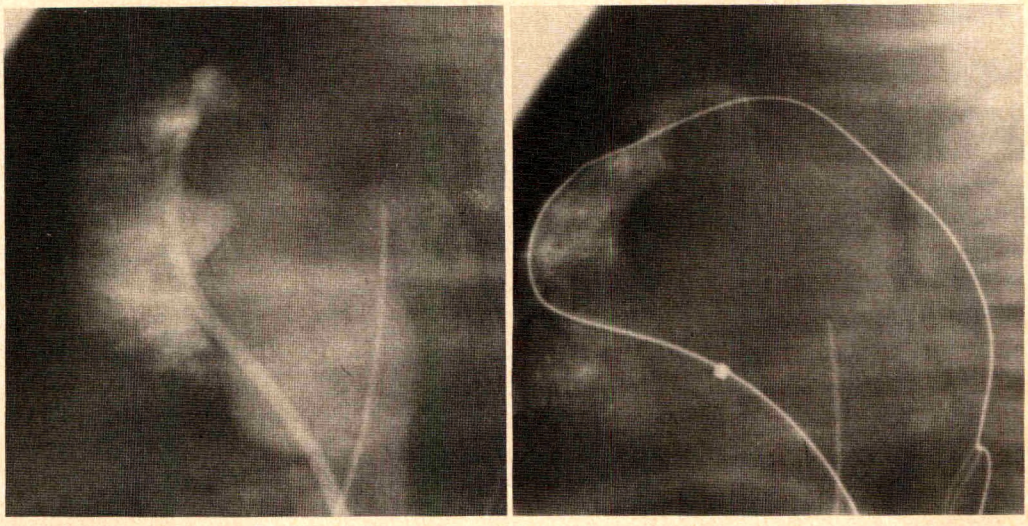


FIGURE 1. ***Left,*** **lateral view of initial right ventricular angiogram. The right ventricle appeared mildly hypoplastic but tripartite, with a well-developed outflow tract. The atretic pulmonary valve membrane appeared thin and mobile. The catheter tip in this angiogram is pointed too cephalad for safe perforation of the valve membrane. Use of a preformed catheter and curving the stiff end of the perforating wire allowed the direction of perforation to be more in line with the orientation of the outflow tract.** ***Right,*** **lateral view of right ventricular angiogram after balloon valvuloplasty. The transductal guidewire was left in place and the snare holding the tip of the wire is seen in the descending aorta. Good prograde flow through an eccentric opening in the atretic valve is demonstrated.**

septum — those with a thin atretic membrane, near normal-sized right ventricle and pulmonary artery, and a ductus arteriosus in the usual position — without surgical intervention. The technique described is technically demanding and not without risks, but we believe that use of a fine wire to perforate the valve, and then controlling the distal tip of the wire to maintain the ability to force a valvuloplasty catheter through the very small opening, should result in a reasonable safety margin in experienced hands compared with the surgical alternatives.

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Catheterizing Modified Blalock-Taussig Shunts and Ascending Aorta to Pulmonary Artery Shunts

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Assessing the anatomy, pressure and resistance of the pulmonary vascular bed is an essential part of the preoperative evaluation of patients with congenital heart disease. In patients with pulmonary atresia or other complex defects when anterograde passage of a catheter into the pulmonary artery is not possible, pulmonary venous wedge pressures have been used to assess the pulmonary arterial pressure, and angiograms recorded close to systemic to pulmonary artery shunts have been used to assess the anatomy of the pulmonary vascular bed. These techniques often do not provide accurate information. It is preferable to directly measure pulmonary artery pressure and pulmonary vascular resistance, and perform angiography in the pulmonary artery. White[1] previously described a technique for catheterizing Blalock-Taussig (B-T) shunts (subclavian artery to pulmonary artery anastomosis) using specially preformed catheters. In this report we describe a method of retrograde catheterization of the pulmonary artery via modified B-T shunts and ascending aorta to pulmonary artery shunts. A number of catheters, Gensini (USCI, Billerica, Massachusetts), pigtail (Cordis, Miami, Florida), GL (Goodale-Lubin, USCI, Tewksbury, Massachusetts), have been used at our institution to enter such shunts. We have found that the shunts may be most easily catheterized using a Cordis Judkins 5Fr right coronary artery catheter with a 4-cm curve.

The patient's right or left femoral artery is entered and a 5Fr or larger sheath is introduced. An angiogram is then recorded in the aortic root to determine the exact location of the shunt. The 5Fr right coronary catheter is introduced and advanced to the arch of the aorta. In the case of left-sided modified B-T shunts, the catheter may be advanced directly to the left subclavian artery. For right-sided shunts, the catheter is manipulated around the arch of the aorta beyond the innominate artery, and is then withdrawn with clockwise rotation so that its tip engages the innominate artery. The catheter is now advanced to the right subclavian artery and just beyond the origin of the modified B-T shunt. For both right- and left-sided shunts a Cook 0.038-mm exchange wire with a 3-mm J curve (Cook, Bloomington, Indiana) is introduced and advanced just beyond the end of the catheter so that its tip points in the direction of the shunt. The catheter is now slowly withdrawn until the wire engages the orifice of the shunt. Clockwise or counterclockwise rotation of the catheter and the wire may be necessary to achieve this. Once the wire has entered the shunt it is usually easily advanced to the ipsilateral pulmonary artery and turned medially so that it can be advanced to the main and contralateral pulmonary artery. In the case of ascending aorta to pulmonary artery shunts the Judkins catheter is advanced to the aortic root. It is then slowly withdrawn with clockwise or counterclockwise rotation so that its tip engages the shunt. The exchange wire may then be introduced. After the exchange wire has been securely positioned in the pulmonary artery, the Judkins catheter may be removed and a 5Fr pigtail catheter (Cordis) is advanced over the wire to the pulmonary artery to obtain angiograms (Figure 1). If the modified B-T shunt arises at an acute angle from the subclavian or innominate artery it may be easier to advance a more flexible catheter such as a 4Fr Cook catheter (Cook, Bloomington, Indiana)

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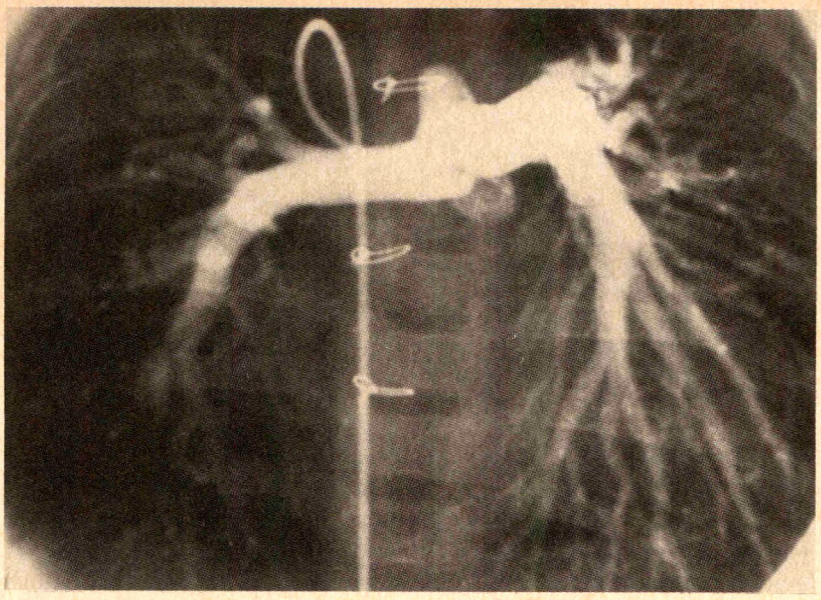


FIGURE 1. Pulmonary artery angiogram in a patient with tetralogy of Fallot, right aortic arch and ascending aorta to main pulmonary artery conduit.

rather than a pigtail catheter over the exchange wire. Occasionally the Judkins catheter can be directly manipulated into the shunt without using a guidewire.

We have been successful in catheterizing the pulmonary artery through a modified B-T shunt or an ascending aorta to pulmonary artery shunt 20 times in 20 patients (1 patient underwent catheterization twice). An attempt to enter the right pulmonary artery through a 5-mm right modified B-T shunt was unsuccessful because of "kinking" of the conduit at its anastomosis with the right pulmonary artery. The mean age of the patients at the time of the catheterization was 43.8 months (range 11.5 to 109) and their mean weight was 13.8 kg (range 6.7 to 28.8). Eight modified B-T shunts and 4 ascending aorta to pulmonary artery shunts have been catheterized using the Judkins catheter. A GL, Gensini, or end-hole balloon catheter (Arrow, Reading, Pennsylvania) was used in the other patients. The patients' diagnoses were tricuspid atresia with or without pulmonary atresia (n = 3), pulmonary atresia with an intact septum or with a ventricular septal defect (n = 4), single ventricle with pulmonary stenosis or atresia (n = 5), tetralogy of Fallot (n = 6), double-outlet right ventricle with pulmonary stenosis (n = 1), and l-transposition of the great arteries with a ventricular septal defect and main pulmonary artery band (n = 1). In the latter 2 patients, anterograde catheterization of the pulmonary artery was unsuccessful. Two patients with 4-mm diameter shunts have undergone catheterization using this technique. Both of these patients had alternate sources of pulmonary flow. One of the 4-mm shunts was an ascending aorta to pulmonary artery shunt. No complications, e.g., worsening hypoxia or dysrhythmia occurred. All patients were given heparin, 50 U/kg, after femoral artery puncture. No patient had vascular complications.

The angulation of the 5Fr Judkins right coronary catheter makes it suitable for entering modified B-T shunts and ascending aorta to pulmonary artery shunts. Because direct access is provided to the pulmonary bed, its hemodynamics may be better evaluated and adequate angiograms obtained. This technique avoids problems associated with other methods of determining pulmonary artery pressures. For example, pulmonary vein wedge pressure recordings may be unreliable and dysrhythmias may be provoked when pulmonary venous wedge pressures are recorded. The diameter of the 5Fr catheter is 1.67 mm; therefore obstruction of 4- or 5-mm shunts is unlikely. However, the technique probably should not be used in patients who have preexisting obstruction of shunts; the patients' pulmonary artery pressure tracings should be observed for damping and the systemic arterial saturation monitored to ensure that the catheter is not obstructing the shunt. The method used by White[1] required specially preformed catheters, whereas we use standard catheters. In addition, White entered classic B-T shunts. These tend to be larger in diameter and arise at a less acute angle than modified B-T shunts, and therefore are more accessible than modified B-T shunts.

We have presented a method of catheterizing surgically created systemic to pulmonary artery conduit shunts in children with cyanotic congenital heart disease. This method provides direct access to the pulmonary vascular bed and accurate information for planning the definitive surgical therapy of these patients.

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Evaluation of Cardiac Tumors in Tuberous Sclerosis by Magnetic Resonance Imaging

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Patients with tuberous sclerosis (TS) develop benign tumors in various organs, such as the brain, kidneys, liver, lungs and heart.[1] Cardiac tumors are an important complication of TS, and can be seen with heart failure, arrhythmias or even sudden death.[1] Magnetic resonance imaging (MRI) has recently come into wide use for the assessment of cardiac tumors.[2] However, there have been no studies published of the MRI evaluation of cardiac tumors in TS. In the present study, the usefulness of MRI was compared with that of 2-dimensional echocardiography in patients with TS.

Fourteen patients with TS, aged 1 to 30 years (median 9), were studied. Echocardiography was performed from parasternal, apical and subcostal windows using a Hewlett-Packard ultrasound instrument (model 77020A) within 3 days before the MRI studies were done. The echocardiographic findings were examined by 2 experienced echocardiographers. If necessary, patients were sedated with chloral hydrate orally or thiopental sodium intravenously, or both. MRI studies were performed using a Signa MR imager (General Electrics, Milwaukee) that was equipped with a superconducting magnet operating at 1.5 tesla. Electrocardiographic gating was used in all patients. The imaging matrix was 256 × 256, signal acquisition was performed twice, and the field of view was 32 or 24 cm depending on the patient's body size. The slice thickness was 5 mm and contiguous slices were obtained. The spin-echo technique was used with a multislice technique. Repetition time was equal to the RR interval of the electrocardiogram (about 500–1,000 ms), with the short echo time being 20 ms and the long echo time being 60 to 80 ms. Imaging was performed in the transverse, sagittal and coronal planes. Both respiratory compensation and spatial presaturation methods[3] were used. The MRI studies were assessed by 2 experienced interpreters without previous knowledge of the results of echocardiography. A cardiac tumor was diagnosed if a circumscribed mass with an intensity dif-

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TABLE I Results of Two-Dimensional Echocardiography and Magnetic Resonance Imaging in Tuberous Sclerosis Patients with Cardiac Tumors

			Magnetic Resonance Imaging				
						Signal Intensity	
Pt. No.	Age (yr & Sex)	2-DE Location	Location	Size (mm)	Character	Short TE	Long TE
1	1 F	RV (VS)	RV (VS)	6 × 14 × 12	Intracavitary	↑	→
		LV (VS)	LV (VS)	10 × 18 × 11	Intracavitary	↑	→
		LVOT	LVOT	7 × 8 × 10	Intracavitary	↑	→
2	3 M	RV (VS)	*	*	*	*	*
3	3 F	RV (VS)	RV (VS)	5 × 7 × 5	Intracavitary	↑	→
		LV (VS)	LV (VS)	10 × 11 × 7	Intracavitary	↑	→
4	5 F	RV (VS)	RV (VS)	10 × 11 × 7	Intracavitary	↑	→
5	6 F	RVAW	RVAW	10 × 10 × 10	Intracavitary	↑	→
6	8 F	*	*	*	*	*	*
7	8 M	*	*	*	*	*	*
8	9 M	RV (VS)	RV (VS)	14 × 16 × 12	Intracavitary	↑	→
		RV (VS)	RV (VS)	10 × 17 × 17	Intracavitary	↑ ↑	↑
		*	LV apex	14 × 38 × 18	Intramural	↑ ↑	↑
9	10 F	*	*	*	*	*	*
10	11 M	*	*	*	*	*	*
11	14 F	VS	VS	4 × 10 × 10	Intramural	↑ ↑	↑
		VS	VS	5 × 10 × 6	Intramural	↑ ↑	↑
12	14 F	RV (VS)	*	*	*	*	*
13	20 F	*	LV apex	7 × 15 × 10	Intramural	↑ ↑	↑
14	30 F	VS	VS	4 × 5 × 5	Intramural	↑ ↑	↑

*Not detected.
2-DE = 2-dimensional echocardiography; LV apex = apex of left ventricle; LVOT = left ventricular outflow tract; LV (VS) = left ventricular side of the ventricular septum; RVAW = right ventricular anterior wall; RV (VS) = right ventricular side of the ventricular septum; TE = echo time; VS = ventricular septum; ↑ = moderately high intensity; ↑ ↑ = very high intensity; → = isointensity.

ferent from the adjacent myocardium was shown in ≥2 views throughout the cardiac cycle by echocardiography or MRI, or both.

The MRI and echocardiographic findings for each patient are listed in Table I. Eight of the 14 patients (57%) had tumors detected by MRI. Five tumors were located on the right ventricular side of the ventricular septum (Figures 1A and 2), 2 were on the left ventricular side of the septum (Figures 1, B and D), and 3 were in the septum itself (Figure 3). There were 2 tumors in the left ventricular apex (Figure 2), 1 in the right ventricular anterior wall, and 1 in the left ventricular outflow tract (Figure 1, E and F).

MRI depicted 2 intramural tumors of the left ventricular apex (patients 8 and 13) (Figure 2), although both of them were missed by echocardiography. However, echocardiography suggested that intracardiac tumors were present in 2 other patients (nos. 2 and 12), whereas MRI indicated that they had prominent papillary muscles.

The signal intensities of the tumors were compared with that of normal myocardium on the short and long echo time images, and the tumors detected by MRI were classified into 2 groups (Table I). Group 1 tumors had a moderately high intensity on short echo time images and showed isointensity on long echo time images (8 tumors) (Figures 1, B and C). Group 2 tumors had a very high intensity on short echo time images and a moderately high intensity on long echo time images (6 tumors) (Figures 2 and 3).

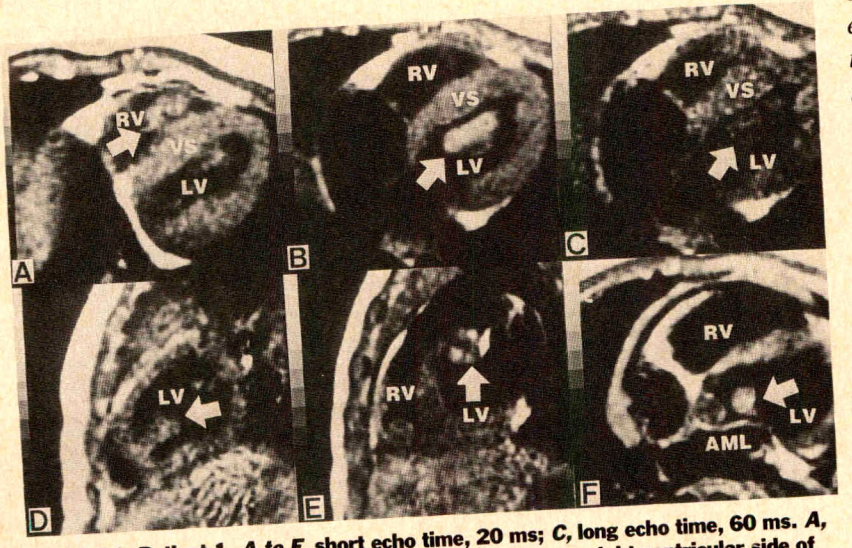


FIGURE 1. Patient 1. *A to F*, short echo time, 20 ms; *C*, long echo time, 60 ms. *A*, transverse plane. An intracavitary tumor is located on the right ventricular side of the ventricular septum (VS). *B*, transverse plane. The tumor is located on the left ventricular side of the ventricular septum of moderately high intensity. *C*, transverse plane. The same tumor shown in *B* is isointense in the long echo time image. *D*, sagittal plane. The same tumor shown in *B* protrudes from the ventricular septum into the left ventricle (LV). *E*, sagittal plane. The tumor is located in the left ventricular outflow tract and is causing subaortic stenosis. *F*, transverse plane. The same tumor shown in *E* is located in the area close to the anterior mitral leaflet (AML). These tumors were suspected to be rhabdomyomas. RV = right ventricle.

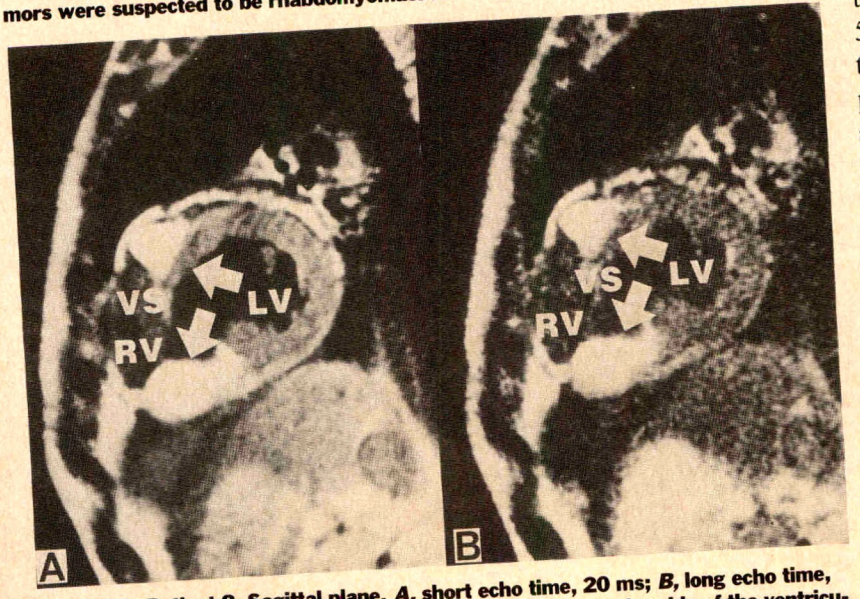


FIGURE 2. Patient 8. Sagittal plane. *A*, short echo time, 20 ms; *B*, long echo time, 80 ms. An intracavitary tumor is located on the right ventricular side of the ventricular septum (VS) and an intramural tumor is located at the left ventricular apex. These tumors show very high intensity in *A* and moderately high intensity in *B*. They were suspected to be lipomas. LV = left ventricle; RV = right ventricle.

Although echocardiography is a primary screening technique for patients with suspected cardiac tumors, this method does not produce good images in some patients because of bone and lung interference. In addition, echocardiography does not appear to be sensitive for detecting intramural tumors.[6] We found that MRI detected 2 intramural tumors that were missed by echocardiography, probably because they were located in the left ventricular apex and good echocardiographic images were

The reported incidence of cardiac tumors in TS ranges from 23 to 58%.[4] In the present study, cardiac tumors were found in 8 of the 14 patients (57%). This incidence was similar to that of the echocardiographic study performed by Bass et al.[5]

not obtained. In contrast, Rienmüller et al[7] reported that MRI was inferior to echocardiography in detecting intramural tumors. The difference might be due to insufficient anesthesia and tachyarrhythmias in some of the patients in their studies. MRI provides higher contrast resolution and a larger field of view without the technical limitations of echocardiography. However, its disadvantages include its high cost, relatively slow rate of image acquisition, and its inability to be used for acutely ill patients. Moreover, although Doppler methods for obtaining flow and pressure information are well established, MRI methods for acquiring this information still remain experimental.

Donegani et al[4] reported in the autopsy series that most cardiac tumors in TS were rhabdomyomas, whereas a few of them were lipomas or fibromas. Histologic confirmation of the tumors was not available in our study, because none of the patients required surgery. However, tissue characterization of the tumors was attempted on the basis of the MRI signal intensities. Six tumors (group 2) were suspected to be lipomas because their signal intensity was very high and was similar to that of fat tissue.[2] Most of these tumors were intramural and they were found in the older patients. These results were similar to those of autopsy studies.[8] The signal intensity of fibroma has been reported to be lower than that of normal myocardium, whereas the intensity of rhabdomyoma is higher than that of the adjacent normal myocardium[2,9] on short echo time images. Eight tumors (group 1) were suspected to be rhabdomyomas because they had this signal intensity pattern. As reported in the autopsy series,[8] these tumors were found in the younger patients. However the MRI intensity pattern of tumors is not always specific. Eight tumors (group 1) showed isointensity on long echo time images in the present study, but Winkler and Higgins[2] reported that 2 rhabdomyomas had relatively high intensity on long echo time images. The reason for this difference is not clear.

In conclusion, MRI provided important additional information that could not be obtained by echocardiography in patients with TS. MRI is especially useful when good echocardiographic images cannot be obtained.

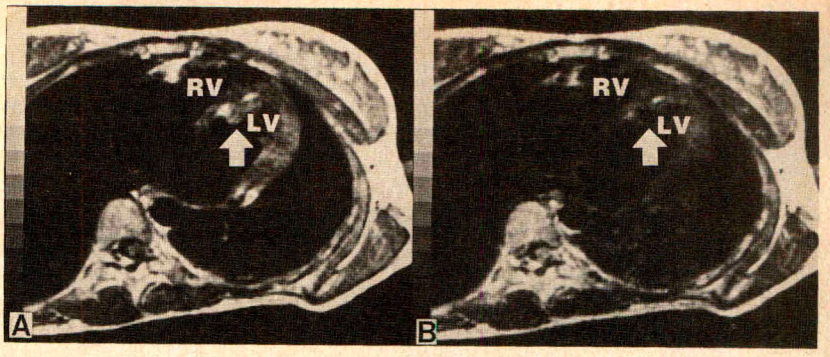


FIGURE 3. Patient 11. Transverse plane. *A*, short echo time, 20 ms; *B*, long echo time, 60 ms. Two intramural tumors located in the ventricular septum show very high intensity in *A* and moderately high intensity in *B*. These tumors were suspected to be lipomas. LV = left ventricle; RV = right ventricle.

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Primary Pulmonary Hypertension for 30 Years

Todd J. Anderson, MD, Erik T. Larsen, MD, D. George Wyse, MD, PhD, and Wanda M. Lester, MD

Primary pulmonary hypertension (PPH) is usually a rapidly fatal condition. Survival from the time of diagnosis is typically <4 years.[1] Clinical but not pathologic data have been reported for 2 patients with PPH of >29 years' duration.[2,3] We report the necropsy findings in a woman who had symptoms of PPH for 30 years.

In 1960 a 23-year-old white woman presented with complaints of fatigue, dyspnea and syncope. She was a smoker, receiving no medications, and her family history was noncontributory. Over the next 10 years, she developed progressive exertional dyspnea. In 1970 she underwent cardiac catheterization, which revealed the following pressures (mm Hg): mean right atrial—7, mean pulmonary capillary wedge—8, and pulmonary arterial—76/38, increasing to 123/61 with exercise. The stroke volume index was 30 ml/beat/m^2 and pulmonary vascular resistance index was 117 mm Hg/liters/min. She was lost to follow-up until 1980, when she presented with peripheral edema and a second episode of syncope. Clinical examination confirmed marked pulmonary hypertension and tricuspid regurgitation; in addition, she had pitting edema to the mid-shin. She was begun on warfarin and hydralazine, with marked but temporary improvement. In 1985, hydralazine was changed to nifedepine, again with transient improvement in dyspnea and edema. In early 1989, she was admitted to the hospital for treatment of supraventricular tachycardia and worsening symptoms. She was begun on digoxin and quinidine. Nifedepine was changed to diltiazem. Atrial fibrillation persisted and quinidine was stopped. She required increasing diuretic therapy to control peripheral edema. In February 1990, she had syncope again and was accepted onto a waiting list for heart-lung transplantation. Cardiac catheterization revealed a grossly dilated right ventricle with marked tricuspid regurgitation. Passage of the catheter into the right ventricle was not possible. Right atrial pressure was 24 mm Hg. She was stable, with dyspnea at rest, until June 1990, when she had a witnessed sudden death at home.

At necropsy, the heart weighed 760 g. The coronary arteries were all <25% narrowed in cross-sectional area. No congenital or valvular abnormalities were found to account for the pulmonary hypertension. Both the right atrium and ventricle were dilated, and the right ventricle was hypertrophied, with wall thickness up to 0.9 cm (Figure 1). The left ventricle was normal. The pulmonary artery was larger in circumference (12 cm) than the ascending aorta (7.2 cm) as measured 1 cm distal to the respective valve rings. Both left and right pulmonary arteries contained loosely adherent thrombi, and the left pulmonary artery was dilated up to 11 cm in circumference adjacent to the lung. Intrapulmonary arteries were atherosclerotic.

Thirty-one sections of lung parenchyma were examined by light microscopy. The medial thickness of muscular pulmonary arteries was increased, measuring up to 16% of the external diameter of the arteries (Figure 2). These arteries were not dilated compared with accompanying bronchi. Prominent cellular intimal thickening was present within muscular arteries,

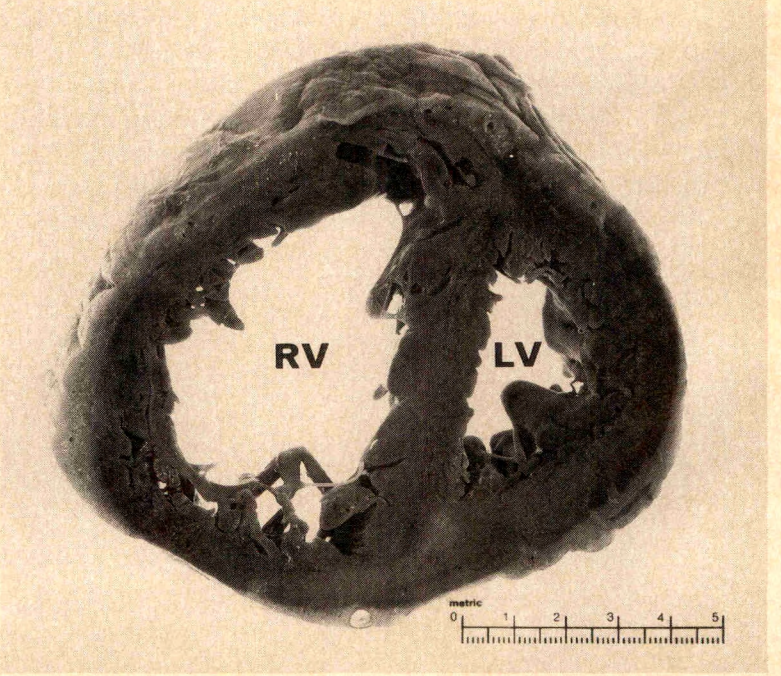


FIGURE 1. Transverse section of heart. The right ventricle (RV) is hypertrophied and dilated. LV = left ventricle.

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mostly eccentric, but no evidence of fresh or recanalized thrombi was found. Neither plexiform lesions nor vasculitis was present. The veins were free of occlusive disease. Sections of left and right main pulmonary arteries confirmed the presence of atherosclerosis and thrombosis.

The histopathologic classification of PPH has evolved over the last 20 years. In 1973 the World Health Organization reported that plexogenic arteriopathy, pulmonary veno-occlusive disease and thromboembolic pulmonary hypertension accounted for most cases of PPH. Some of the difficulties with this terminology were reviewed recently[4] and are exemplified[4] by our patient, who did not have plexogenic lesions, pulmonary veno-occlusive disease or pulmonary thromboemboli. The National Heart, Lung, and Blood Institute PPH Registry has recently developed a light microscopic classification of PPH.[5] According to this classification, our patient had primary pulmonary arteriopathy with intimal fibrosis and medial hypertrophy. Only 4 of 58 patients in the Registry had similar pathology, so clinicopathologic correlation could not be performed.

In a recent study[6] of 19 PPH patients that evaluated lung pathology, response to vasodilators, and survival, 2 of the 4 hemodynamic responders to vasodilator drugs had medial hypertrophy and mild intimal fibrosis in the absence of plexiform lesions and thrombi. Extensive medial fibrosis was associated with a poor response to vasodilators. Our patient did not have medial fibrosis and did have a good clinical response to vasodilators.



FIGURE 2. Section of lung. A medium-sized pulmonary artery *(arrow)* has medial and concentric cellular intimal thickening (Movat stain, ×165, reduced 48%).

Although the clinical significance of PPH with medial hypertrophy and intimal thickening in the absence of plexogenic lesions and thrombi is not yet certain, the 30-year duration of PPH in our patient suggests that it may be associated with long survival.

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Rupture of the Outer Partition of Aortic Dissection During Transesophageal Echocardiography

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Transesophageal echocardiography (TEE) has gained widespread clinical acceptance as a cardiovascular imaging technique.[1] Its reported accuracy and ease of performance may make TEE the procedure of choice for the evaluation of thoracic aortic aneurysms.[2] The safety of this procedure has been well demonstrated, and serious complications have rarely been noted.[3,4] We report an unusual case in which an aortic root aneurysm with a DeBakey type I dissection ruptured during a TEE procedure, resulting in cardiac tamponade and death.

A 26-year-old man without previous medical problems presented with sharp substernal chest pain radiating to the jaw. It was associated with dyspnea and vomiting, and began while running. Physical examination revealed a blood pressure of 108/78 mm Hg, a heart rate of 106 beats/min, and a respiratory rate of 18 breaths/min. The right carotid pulse was diminished. No murmurs or gallops were noted. The palate had a high arch, suggesting Marfan's syndrome, but neither arachnodactyly, an elongated arm span, nor ophthalmic abnormalities were present.

A chest roentgenogram was remarkable for a widened mediastinum. The electrocardiogram was normal. A transthoracic echocardiogram revealed a 7-cm diameter aortic root aneurysm (Figures 1 and 2), with a dissection involving the ascending and descending portions of the aortic arch. The aortic valve was bicuspid, but neither stenotic nor regurgitant. A 3-mm posterior pericardial effusion was present. Aortography confirmed the presence of a DeBakey type I dissection with innominate artery involvement.

While awaiting surgery, the patient developed mid-back pain. TEE was performed to redefine the aortic pathology. After topical anesthesia (Cetacaine®) and light sedation (midazolam hydrochloride), a TEE probe (Hewlett-

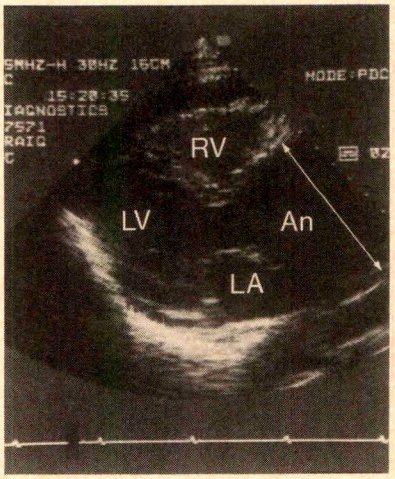


FIGURE 1. Two-dimensional echocardiographic parasternal long-axis view revealing a 7-cm aneurysm (An) involving the aortic root *(arrows)*. LA = left atrium; LV = left ventricle; RV = right ventricle.

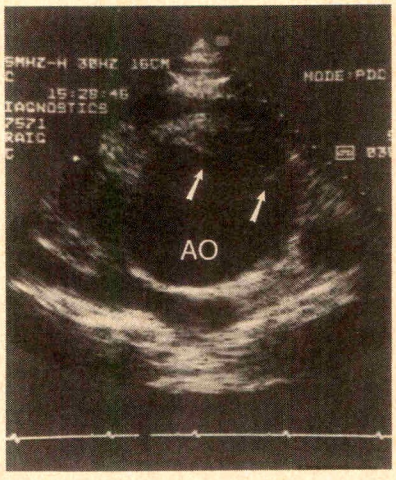


FIGURE 2. Two-dimensional echocardiographic parasternal short-axis view of the aortic root (AO) revealing aneurysmal dilatation with intimal flap *(arrows)*.

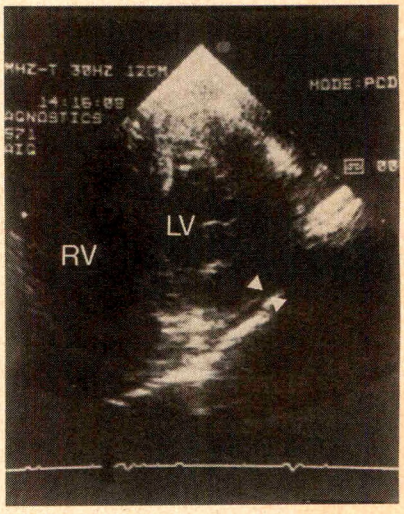


FIGURE 3. Initial transesophageal echocardiographic transgastric short-axis scan revealing small pericardial effusion *(arrows)*. Abbreviations as in Figure 1.

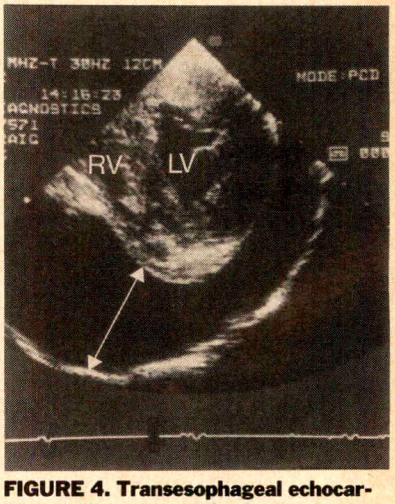


FIGURE 4. Transesophageal echocardiographic transgastric short-axis scan recorded 15 seconds after Figure 3. Note large pericardial effusion *(arrows)* with right ventricular diastolic collapse and small left ventricular cavity. Abbreviations as in Figure 1.

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Packard model 21362A) with a 5.0-MHz transducer was advanced without difficulty into the transgastric short-axis position. Initial images confirmed a small pericardial effusion (Figure 3). At this time, the patient retched and had an episode of respiratory distress that was initially attributed to gastric irritation from endoscope manipulation. However, within seconds of this episode, the pericardial effusion rapidly enlarged, with resultant cardiac tamponade (Figure 4). Despite emergency pericardiocentesis and a subxiphoid pericardial window, refractory tamponade persisted. Autopsy confirmed an aortic root aneurysm with a DeBakey type I dissection. A large posterior aortic tear communicated with the pericardium, which contained 350 ml of thrombus.

TEE provides a rapid, accurate method for the diagnosis and evaluation of thoracic aortic aneurysms. It is possible that this imaging modality will emerge as the procedure of choice for diagnosing aortic dissection.[2] Complications and adverse effects related to the use of TEE are noted in <1% of procedures,[3] and are infrequent even among critically ill patients.[4] Reported complications include transient atrioventricular block, nonsustained ventricular tachycardia, arterial hypoxemia, bronchospasm and transient myocardial ischemia.[2] Esophageal damage is also a potential problem.[5] However, an association between aortic aneurysm rupture and TEE has not previously been noted.

Spontaneous aneurysm rupture unrelated to TEE (i.e., a pseudocomplication) is possible in our patient. However, the TEE procedure may have precipitated this event in a number of ways. Geibel et al[3] noted that 77% of 51 patients undergoing TEE had an increase in systolic blood pressure averaging 16 mm Hg. However, increases as great as 51 mm Hg were noted. Also, 32 of 46 patients in sinus rhythm exhibited an increase in heart rate averaging 8 beats/min. It is possible that an increase in blood pressure and heart rate, perhaps related to the gag reflex, gastrointestinal irritation or anxiety, triggered the aortic aneurysm rupture in our patient. A mechanical effect of TEE must also be considered. Urbanowicz et al[5] noted that contact pressures between a TEE probe and the esophagus, although generally <17 mm Hg, could reach 60 mm Hg in individual patients. Such a high pressure exerted in the region of a large aortic aneurysm could have contributed to its rupture.

The relation between the aortic aneurysm rupture and TEE in this case is conjectural. The events may have been unrelated, representing a pseudocomplication. However, hemodynamic and mechanical effects of TEE may have contributed to the aneurysm rupture. In patients with aortic dissection undergoing TEE, efforts should be made to minimize these hemodynamic and mechanical effects. These efforts should include adequate anesthesia and sedation to suppress the gag reflex and minimize gastric reactions,[6] and exertion of the minimal amount of torque on the TEE controls compatible with adequate visualization.[5]

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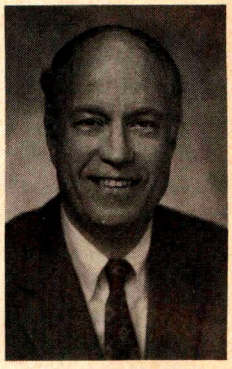
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Human Records and a Tribute to the *Guinness Book of World Records*

In 1953 or 1954, Sir Hugh Beaver, the managing director of United Kingdom's largest brewery, Guinness, Ltd, while at a grouse shoot at the Guinness estate, missed a golden plover with his shot. At dinner that evening Beaver initiated a discussion on the fastest game birds and observed that none in attendance had any idea of their flying speed. Beaver recognized an opportunity and approached the Guinness board of directors about producing a record book. Lord Iveach, the company's chief executive officer, liked the idea and the McWhirter twins, Norris and Robert, were recommended as potential authors. The first edition of the *Guinness Book of World Records* appeared in the United Kingdom in 1955 and subsequently 262 editions in 35 languages have appeared. By 1974, the *Guinness Book of World Records* became the top-selling copyright book in publishing history. By 1989, global sales surpassed 60 million. The present book[1] is the 29th US edition, the first of which appeared in 1956. The book has become *the* authoritative source of records in nearly all fields of human and non-human endeavor, and now the Guinness company publishes about 40 books of various sorts each year.

Tallest human being: Robert Pershing Wadlow (1918–1940) was measured in 1940 by Doctors C.M. Charles and Cyril MacBryde of the Washington University School of Medicine to be 8 feet 11.1 inches (272 cm) tall and to have an arm span of 9 feet 5.75 inches (289 cm). At age 21 he reached his maximal weight (491 pounds [223 kg]). Because he was still growing, he probably would have reached a height of >9 feet (>274 cm) had he lived longer than 22 years. His shoes were size 37AA (18.5 inches [47 cm]), and his hands measured 12.75 inches (32 cm) from the wrist to the tip of the middle finger. At least 10 other human beings, 9 men, were known to be >8 feet (>244 cm) tall and their life spans ranged from 18 to 56 years (mean 37); only 2 were over 50 years of age and only 4, over 40 years of age. At least 7 of the 11 humans >8 feet tall had acromegaly. Thus, tall bodies, just like large hearts, are not associated with long survival.

Shortest adult human being: Pauline Masters (1876–1895), who died at age 19 years, reached a height of only 23.2 inches (59 cm) and her peak weight was 9 pounds (4.1 kg). The shortest recorded adult male dwarf was Calvin Phillips (1791–1812) who lived 21 years and at age 19 he was only 26.5 inches (67 cm) tall and weighed slightly less than 12 pounds (5.4 kg). For comparison, the average length of newborn babies is about 19 inches (48 cm). The most famous midget was Charles Sherwood Stratton, alias "General Tom Thumb" (1838–1885) who toured with the P.T. Barnum circus. He grew to a height of 40 inches (102 cm) and weighed 70 pounds (32 kg). At age 25, he married Lavinia Warren, 32 inches (81 cm) tall. At their wedding reception, the bridal couple stood on top of a piano to greet the 2,000 guests, and then cut the wedding cake that weighed more than they did together.



Heaviest human being: Jon Brower Minnoch (1941–1983) weighed approximately 1,400 pounds (635 kg) when in congestive heart failure at age 37 years. When not in heart failure the 73-inch (185 cm) tall man usually weighed 800 to 900 pounds. His wife weighed 110 pounds (50 kg) when he weighed 1,300 pounds (590 kg), a 12-fold difference. At least 5 other men have been reported to weigh >1,000 pounds (>454 kg). The heaviest woman was Percy Pearl Washington (__-1972) who weighed approximately 880 pounds (399 kg) and she was 72 inches (183 cm) tall. The largest waist measured 119 inches (302 cm) in a 1,200-pound man.

Lightest human being: The thinnest recorded adults of normal height are those with anorexia nervosa. One such person was Emma Shaller (1868–1890) who weighed 45 pounds (20 kg) and she was 62 inches (157 cm) tall. Edward C. Hagner (1892–1962), alias Eddie Masher ("Skeleton Dude"), was 67 inches (170 cm) tall and weighed 48 pounds (22 kg). The smallest adult waist among women of normal stature measured 13 inches (33 cm) and belonged to the French actress Mlle. Polaire (1881–1939).

Heaviest organ: The *skin* is the heaviest, averaging about 2,675 g. The heaviest internal organ is the *liver* which normally weighs about 1,700 g. The adult male *brain* averages about 1,425 g, and the adult female's, about 1,265 g. There is no correlation between intelligence and brain size. Human brains appear to be getting bigger. The heaviest brain weight recorded was 2,050 g in a 50-year-old man. The normal adult *heart* weighs <400 g. The largest reported was >1,800 g but I suspect the weight was inaccurate.[2] I have seen approximately 35 hearts weighing >1,000 g. Most had aortic regurgitation. Only 1 patient was a woman and she had the largest heart I have seen — 1,260 g and she weighed 123 pounds

(56 kg), stood 63 inches (160 cm) tall, and had hypertrophic cardiomyopathy.[3]

Births and babies: The most children born to one mother is 69. In 27 confinements she gave birth to 16 pairs of twins, 7 sets of triplets and 4 sets of quadruplets. At least 67 who survived infancy were born in the USSR from 1725 to 1765. The oldest medically verified mother was Ruth Alice Kistler (1899–1982) who was 57 years and 129 days old when she gave birth to a daughter. Dr. E. Derasse in 1891 reported in a French medical journal a 59-year and 5-month-old mother who birthed a healthy baby. The woman already had a married daughter aged 40 years. Long pregnancies of 14, 16 and 36 months have been reported. In 1961 a Burmese woman aged 54 years was delivered by Cesarean section of a 3 pound (1.4 kg) calcified fetus after 25 years' gestation. She had gone into labor in 1936, but no child was born. The most premature surviving newborn was 128 days premature and weighed 1.4 pounds (0.6 kg).

The biggest surviving baby weighed 22.5 pounds (10 kg). Babies surviving <24 hours have had recorded weights of 24 pounds (11 kg), 25 pounds (11 kg) and 29 pounds (13 kg). The lowest birth weight recorded for a surviving infant is 0.6 pound (0.28 kg). The highest number of infants reported at a single birth was 10 (decaplets). The highest number surviving was 6 of 6. The heaviest quadruplets together weighed 22.8 pounds (10.3 kg); the heaviest triplets 26.4 pounds (12 kg); and the heaviest twins together, 27.75 pounds (12.6 kg).

Longevity: No subject is more obscured by vanity, deceit, falsehood and fraud than human longevity. Claims apparently are generally made on behalf of the very aged rather than *by* them. The greatest *authenticated* age to which any human has ever lived is 120 years and 237 days. He was born in Japan in June 1865 and died of pneumonia in February 1986. Thirty other persons have had authenticated life spans of 105 to 115 years.

Hands, feet and hair: *Fingernails*, which grow about 0.05 cm a week, in an Indian man in aggregate in one hand measured 173 inches (439 cm): 102 cm thumb, 77 cm first finger, 86 cm second and third fingers, and 88 cm fourth finger. He did not cut his fingernails from 1952 to 1990. The largest *feet* have required size 22 sandals. Human *hair*, which grows at a rate of 1.3 cm a month, if left uncut will usually grow to a maximum of 2 to 3 feet. Hair measuring 12 feet (3.7 meters) long has been reported. The longest *beard* measured 17.5 feet (5.3 meters). The longest *mustache* reached 9.5 feet (2.9 meters).

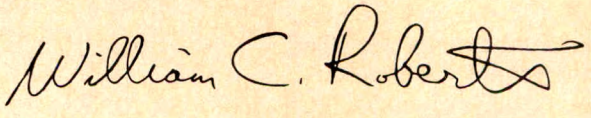
Best memory: A man recited 16,000 pages of the Buddhist canonical texts; another man memorized >15,000 telephone numbers; another man memorized on a single sighting a random sequence of 30 separate packs of cards (1,560) that had been shuffled together.

Body temperature: The highest body temperature recorded with survival was 116°F, and the lowest, 61°F.

Most common diseases: The most common noncontagious disease is gingivitis, which afflicts 80% of the US population; the commonest contagious disease is acute nasopharyngitis.

Medical extremes: The heart of a Norwegian fisherman, who fell overboard into icy waters, stopped for 4 hours while his temperature fell to 77°F. He made a full recovery. A woman was in coma for the last 44 years of her life. A woman was in an "iron lung" for the last 37 years of her life. A man hiccupped 20 to 40 times a minute for 68 years without a cure. A woman sneezed for 978 days; she sneezed an estimated 1 million times during the first 365 days of the attack. (The highest speed at which expelled sneezed particles have ever been measured to travel is 104 miles/hour.) The highest sound level recorded by any chronic snorer is a peak of 90 decibels. (A city traffic bylaw for acceptable noise where the snorer resided was 80 decibels.) The longest recorded period for which a person has voluntarily gone without sleep is nearly 454 hours in a man who sat in a rocking chair during the sleeplessness period. Some persons have been found to have not slept for years (total insomnia — chronic colestites). The longest period for a person to remain motionless continuously is 24 hours — he sat on a motorcycle. The worst reported case of compulsive swallowing involved a woman who was found to have 2,533 objects in her stomach, including 947 bent pins. The longest period for which anyone has gone without food is 382 days. Most well-nourished individuals can survive without medical consequences on a diet of sugar and water for about 30 days. The longest recorded survival without food *and* water is 18 days. The longest stay in a hospital is >99 years. The highest recorded number of total pills swallowed by a patient is 565,939 during a 21-year period. The most injections was by a woman with diabetes mellitus who gave herself an estimated 61,123 insulin injections over a 59-year period.

This is enough. You get the idea.



William Clifford Roberts, MD
Editor in Chief

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A Possible Interaction Between Heparin and Intravenous Nitroglycerin

Zahger et al[1] retrospectively found that patients treated with streptokinase for acute myocardial infarction seemed to be partially resistant to anticoagulation. This is an important finding, as it has already been reported that simultaneous infusion of heparin and streptokinase speeds up the appearance of signs of reperfusion and reduces infarct size.[2]

However, an aspect not discussed—other than the possibility that patients were hypercoaguable—was the effect of concomitant drug therapy on heparin. The authors make clear that many patients were indeed receiving nitrates; however, it is not clear whether these were oral or intravenous preparations. A recent series of brief reports suggest that intravenous nitroglycerin may induce heparin resistance and emphasize the need for frequent monitoring of the activated partial thromboplastin time both during the intravenous nitroglycerin infusion and after its cessation.[3,4] However, details to date are incomplete and only suggest that such an interaction does occur. Another study[5] has been unable to show that nitroglycerin does indeed induce heparin resistance. The mechanism of such resistance has been postulated to be an effect of high-dose intravenous nitroglycerin on anti-thrombin III.[6]

Clearly, this is only a possible contributory factor in the etiology of the resistance to anticoagulation; however, its importance should not be underestimated. As well as the laboratory evidence by Owen et al[7] suggesting that elevated levels of fibrinopeptide A after thrombolysis imply ongoing active thrombosis, we now have recent evidence from angioscopy studies performed after myocardial infarction suggesting that intracoronary thrombus may well be present for 2 weeks after acute myocardial infarction.[8]

Clearly, what will be required to answer these questions are a series of complex trials that do indeed assess the effect of intravenous nitroglycerin on the activated partial thromboplastin time heparin effect at varying dose levels of intravenous nitroglycerin.

A final point to consider is that the activated partial thromboplastin time may not actually be the ideal parameter with which to monitor the effect of heparin on its own, and that the activated clotting time, which is a simple and easy method to use, may be more appropriate.[9] The activated clotting time should be monitored by measurement of the activated clotting time of the arterial blood. Although the activated partial thromboplastin time is a popular laboratory test and is considered to be sensitive, it is time-consuming and cannot be easily performed outside the laboratory. Furthermore, its relation to the heparin concentration is linear only over a small heparin dosage range.[10]

Chris Bushe, MB, BS
Elizabeth Wales, BSc
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12 November 1990

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REPLY: Bushe and Wales rightly point out that intravenous nitroglycerin has been shown by a number of investigators to cause heparin resistance. In our patients, nitrates were initially given in the form of intravenous nitroglycerin, which was replaced in 24 to 48 hours by an oral preparation. As shown in our work, the use of nitrates was not statistically different between the 2 groups and therefore the heparin resistance that was found can not be attributed to nitroglycerin.

We agree that the optimal test for the monitoring of heparin anticoagulation has not been determined, and the activated partial thromboplastin time may not be the best one. Nevertheless, the activated partial thromboplastin time remains a widely used test and many, if not most, clinicians adjust heparin doses according to this test. It would be interesting to evaluate the response to heparin after thrombolysis by other tests of anticoagulation as well.

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17 December 1990

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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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* Defined as a combination of definite coronary death and/or definite myocardial infarction. $P = .013$; 95% CI 13.3-111.5.

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